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Major depression is a serious disorder whose lifetime prevalence of 16.2% in the USA is being increasingly echoed in contrasting cultures, eg, Japan and China. The apparent increase requires qualification: people may be readier to discuss psychological problems than previously, and early studies were probably underestimates. In addition, differential memory distorts retrospective estimates of lifetime prevalence. People forget distant episodes of depression and inflate current episodes: follow-up of patients hospitalized for depression found that 25 years later only half could recall sufficient symptoms to justify a diagnosis of major depression.

Major depression is associated with substantial social and even physical dysfunction, significantly more than some chronic medical conditions, eg, diabetes. Onset is typically in the teens and twenties and the course commonly recurrent or chronic, with depressive episodes occupying 20% of postdiagnosis life. Unsurprisingly, therefore, major depressive disorder is now the leading cause of disability in those of active working age. Some 10% to 15% of depressed patients eventually commit suicide. A meta-analysis found a standard mortality rate, calculated by comparing the suicide rate in a specific group with that in the general population, of 21.2 among depressives; mood disorders shorten life by 10 years from the combined effect of increased suicide risk and increased physical illness.

Not only do current antidepressants not “cure” the underlying condition, they are also only moderately effective in relieving symptoms during episodes. A National Institute of Mental Health (NIMH) follow-up of 431 patients seeking treatment found that 12% remained chronically depressed over 5 years, while 55% had suffered a relapse or recurrence, and only one third remained healthy; after 15 years, 82% had had a recurrence, 6% remained chronically depressed, and only 12% remained healthy. Given sufficiently long and careful follow-up, almost all those treated for major depression will fail to recover, or suffer a recurrence.

Nevertheless, there is an overwhelming case for providing appropriate treatment for depression, on both personal and socioeconomic grounds. Yet undertreatment remains widespread. Of the 17% with major depression identified in a European survey of 78 000 adults, 69% were receiving no medical treatment, 43% had not even consulted a doctor, and under 8% were on an antidepressant. In addition, antidepressant treatment is often suboptimal: in a survey of 1 million patients in primary care, 89% were receiving a subtherapeutic dose of tricyclic antidepressant (TCA). Fortunately, underprescribing has become less common with newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs), which are only marketed at therapeutic doses.

Poor treatment response is often due to poor patient compliance: 30% of primary care patients never fill their first prescription, while a further 25% to 33% stop treatment in the first month, and 62% fail to inform their physician accordingly. As a result, treatment duration in 55% to 63% of cases is less than the minimum consensus recommendation of 6 months post remission. However, even in well-conducted studies with various classes of antidepressant administered for the 6 to 8 weeks generally thought sufficient to show a drug/placebo difference, nonresponse rates average 30% to 40%.
Developments of antidepressants

The presumed mechanism of action of both monoamine oxidase inhibitors (MAOIs) and TCAs was that they blocked the reuptake of the neurotransmitter monoamines, norepinephrine and serotonin (5-HT), thus increasing their availability in the synaptic cleft. Depression was presumed due to subnormal neurotransmitter levels. Although oversimple and incomplete, this theory provided a broad basis for the development of most subsequent antidepressants. Research focused on the design of compounds with greater selectivity for either monoamine, hence with fewer side effects. Maprotiline and reboxetine were examples of selective norepinephrine reuptake inhibitors (SNRIs). But most effort concentrated on the development of SSRIs, culminating in fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram, which now dominate the antidepressant market.

Several TCAs were found to act on 5-HT2 receptors: amitriptyline both blocked 5-HT reuptake and was a 5-HT2 antagonist. This inspired the development of 5-HT2 antagonists such as trazodone, followed by compounds more selective still, acting on 5-HT2 receptor subtypes, such as agomelatine, a 5-HT2C antagonist and melatonin M1/M2 agonist, and mianserin and mirtazapine, which are 5-HT2A and 5-HT2C receptor antagonists as well as α2 antagonists and 5-HT1A and 5-HT3 antagonists.

Superiority of particular antidepressants

Clinical trials of antidepressants have failed to demonstrate a consistently superior response to active treatment versus placebo. This is due, irrespective of the inherent (in)efficacy of the antidepressants themselves, to the inappropriate design and conduct of the studies, and some major theoretical and practical obstacles. One important failing has been inadequate power, while a number of “unsuccessful” studies have never been published. Smaller studies demonstrating significant efficacy were often confined to severely depressed inpatients, whereas the move to more realistic community-based studies recruited many patients with mild depression for which drug/placebo difference was difficult to demonstrate. Even the diagnostic criteria for major depressive disorder have proved inadequate, with particular regard to illness duration. Whereas the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria require only 2 weeks, compatible with a self-limiting disorder, investigators have long since increased the minimum episode duration to 1 month to qualify for study inclusion.

Drug/drug difference is even more difficult to demonstrate. SSRIs may be safer and better tolerated than TCAs, but they appeared significantly less effective than conventional clomipramine in one key study. Despite its methodological weaknesses, this study suggested that selectivity for the serotonin system might not be universally beneficial. A plausible conclusion was that selective antidepressants would only be effective in patients with the relevant monoamine deficiency, a theory bolstered by the reports from several subsequent studies that SNRIs such as venlafaxine were more effective than SSRIs, which were themselves significantly better than placebo. However, this conclusion failed to secure consensus conviction, even with the backing of a meta-analysis, due to an array of methodological failings.

A rare opportunity for valid interdrug meta-analysis was afforded by the pooled studies of the SSRIs escitalopram and citalopram, in that all were of the same 8-week duration and used the Montgomery and Asberg Depression Rating Scale (MADRS): several meta-analyses across a variety of conditions reached the consensus conclusion that escitalopram was the more effective agent.

Early onset of response

A well-recognized shortcoming of antidepressants is that significant difference from placebo can only be identified reliably some 6 weeks after initiating treatment. The delay is potentially dangerous since suicide risk is highest in the early treatment period when severity is greatest. Absence of rapid positive feedback also encourages noncompliance. Earlier onset of effect would therefore be welcome. Unfortunately, however, virtually no studies have investigated this aspect in individual antidepressants. Retrospective review of placebo-controlled studies with venlafaxine indicates simply that response before 2 weeks is seen with early rapid escalation to high doses, while comparative studies have suggested that escitalopram induces a more rapid response than citalopram.

Efficacy of specific symptoms

Some symptoms improve faster with one antidepressant than another.
Sleep
Antidepressants with antihistaminic activity, eg, amitriptyline and mirtazapine, improve sleep early in treatment, but at the cost of compromised daytime alertness and impaired concentration. 5-HT2 antagonists, eg, nefazodone, improve sleep with no such penalty, as does the melatoninergic agonist and selective 5-HT2C antagonist agomelatine.

Pain and somatic symptoms
SNRIs may be more effective in relieving pain syndromes. Thus, venlafaxine was superior to placebo in diabetic neuropathy. In fact, SNRIs may be more effective on the somatic symptoms of depression generally.11 While these are not the core symptoms of the disorder, they may explain the apparent advantage of SNRIs over SSRIs, particularly when remission is assessed using the Hamilton Depression Rating Scale (HDRS) with its overrepresentation of somatic symptoms. The advantage may be less apparent when using a core symptoms scale such as the MADRS.

Discontinuation of medication
Early studies with TCAs established that abrupt treatment withdrawal provoked a syndrome of nausea, vomiting, headaches, giddiness, chills, weakness, and musculoskeletal pain in some patients. Symptoms were transient, maximal in the first week and declined thereafter, rarely interfering with function.

A discontinuation syndrome was also reported with the SSRIs, whether withdrawal was gradual or abrupt. Its timing appeared dependent on the half-life of the compound concerned and any active metabolite. With fluoxetine, for example, the discontinuation syndrome may appear after 4 weeks, whereas with paroxetine it is maximal in the first week. A consistent finding has been that the syndrome is more frequent with paroxetine than with either sertraline or fluoxetine,14 comprising insomnia, dreaming, muscle aches, dizziness, chills, runny nose, nausea, and diarrhea.

The only antidepressant not associated with a discontinuation syndrome is agomelatine.15 This is a distinct advantage in that many patients receiving antidepressants are erratic and forget to take their medication over a few days during a course of treatment and would therefore be expected to suffer discontinuation symptoms.

Suicide
Suicide risk is highest early in treatment and related to illness severity. The best predictor is a history of a previous attempt, although this is absent in over half of suicides. Long-term follow-up has shown that antidepressants reduce suicide risk 3-fold in unipolar major depression,16 a statistic confirmed by epidemiological studies in Swedish adults and American adolescents.

Being a rare event in clinical studies, suicide risk for an individual drug cannot be assessed even from the large datasets contained in the submissions to drug regulatory authorities. However, a recent meta-analysis of data on over 40 000 patients submitted to licensing authorities showed nonsignificantly fewer suicides with SSRIs compared with placebo.17 A definitive comparison would require the inclusion of millions of patients in placebo-controlled studies.

Results for suicidal thoughts recorded as an adverse event have been similar. Since such thoughts are measured as part of the pivotal depression severity rating scales, they provide the best basis for assessment. Several antidepressants, including imipramine, paroxetine, and escitalopram, are significantly more effective than placebo in protecting against the emergence of suicidal thoughts.18

Safety
Side effects are a major cause of treatment noncompliance. TCAs are especially disadvantaged in this regard, having a broad range of pharmacologic actions in addition to their activity on the norepinephrine and serotonin systems. Effects on muscarinic receptors produce anticholinergic reactions such as dry mouth, blurred vision, constipation, urinary hesitancy, and cognitive deficits, while α1-adrenergic receptor effects are responsible for the dizziness and hypotension that are a particular problem in the elderly because of falls and fractures. Histamine effects cause sedation and poor concentration. The cumulative result is poor tolerability and compromised treatment.

The absence of similar receptor effects explains why SSRIs should be better tolerated, with fewer premature treatment discontinuations.19 However, SSRIs have several characteristic serotonergic side effects; they produce unwanted gastrointestinal effects, for example, nausea and vomiting. Some SSRIs, eg, fluoxetine, cause increased agitation and nervousness, particularly at the
start of treatment. Their sexual side effects include anorgasmia in women and delayed ejaculation in men. There appears to be some tolerance of the nausea, but less of the sexual side effects. Some antidepressants have been shown to have fewer sexual side effects, e.g., nefazodone, possibly due to its 5-HT2 antagonist properties. Bupropion enjoys a similar advantage over SSRIs, although it not licensed as an antidepressant in Europe. Agomelatine appears relatively free of sexual side effects: a specific study found it significantly superior to venlafaxine in patients in remission. There is also evidence that the 5-HT2 antagonist mirtazapine is largely unassociated with sexual dysfunction.

SNRIs are associated with all the SSRI side effects plus some norepinephrine-related effects such as dry mouth, constipation, and increased heart rate. Thus, high-dose venlafaxine is likely to cause excess serotoninergic effects. Venlafaxine is also associated with increased blood pressure and cholesterol, and this must be taken into account when prescribing. Duloxetine is licensed at a low dose specifically to reduce the risk of excess side effects. Both venlafaxine and duloxetine appear to be less well tolerated than SSRIs.

Conclusion
Depression is a common and disabling disorder that places a substantial burden on patients, their relatives and friends, and society as a whole. It is also dangerous, being associated with increased morbidity and mortality, including from suicide. Depression shortens life by an average of one decade. The available treatments are largely effective, but their use is compromised by poor tolerability and low adherence. Very few depressed individuals receive treatment and, of those who do, few are prescribed an adequate dose for long enough to secure a full response. There is a clear need for treatments that are more effective, more rapidly effective, and better tolerated. They would reduce the number of patients who have a poor or inadequate response and leave fewer patients with resistant depression. Poor compliance with medication and premature termination of treatment currently compromise the chance of recovery. Antidepressants with a faster onset of action would be expected to bring larger numbers of depressed patients to full remission.

REFERENCES

Keywords: antidepressant; tricyclic antidepressant; selective serotonin reuptake inhibitor; norepinephrine; melatonin

A DÉPRESSION MAJEURE EST UNE MALADIE GRAVE DONT LA prévalence au cours de la vie atteint 16,2 % aux États-Unis et qui s’approche progressivement de cette valeur dans des cultures très différentes, par exemple au Japon et en Chine. Cette augmentation apparente nécessite d’être nuancée : les personnes semblent plus enclines à discuter de leurs problèmes psychologiques qu’auparavant et les études antérieures ont probablement sous-estimé l’importance de cette maladie. En outre, la mémoire, sélective, tend vraisemblablement à fausser les estimations rétrospectives de la prévalence au cours de la vie. Les personnes ont tendance à oublier des épisodes de dépression lointains et à exagérer les épisodes actuels : le suivi de patients hospitalisés pour dépression a permis de déterminer que, 25 ans plus tard, seulement la moitié des patients pouvait se rappeler de symptômes suffisants pour justifier un diagnostic de dépression majeure.

La dépression majeure est associée à un dysfonctionnement social et même physique important, qui dépasse de manière significative celui provoqué par certaines affections médicales chroniques, par exemple le diabète. Le déclenchement survient généralement au cours de l’adolescence et au début de l’âge adulte, et son déroulement est fréquemment récurrent ou chronique, avec des épisodes dépressifs occupant 20 % de la durée de vie qui suit le diagnostic initial. Par conséquent, il n’est pas surprenant de constater que le trouble dépressif majeur soit la principale cause d’incapacité observée pendant la vie active. Chez environ 10 à 15 % des patients la dépression aboutit au suicide. Une méta-analyse a établi un taux de mortalité standard, calculé en comparant le taux de suicide dans un groupe spécifique avec celui de la population générale, égal à 21,2 chez les dépressifs ; les troubles de l’humeur raccourcissent la vie de 10 ans à cause de l’effet combiné d’une augmentation du risque de suicide et d’une aggravation des maladies physiques.

Non seulement les antidépresseurs actuels ne « guérissent » pas la maladie sous-jacente, mais ils ne sont également que modérément efficaces pour soulager les symptômes au cours des épisodes dépressifs. Un suivi de l’Institut National de la Santé Mentale (National Institute of Mental Health, NIMH) effectué sur 431 patients en demande thérapeutique a montré que 12 % de ceux-ci restaient déprimés de manière chronique pendant 5 ans, tandis que 55 % d’entre eux avaient présenté une récidive ou une rechute, et seulement un tiers restait en bonne santé ; après 15 ans, 82 % avaient subi une rechute, 6 % souffraient toujours d’une dépression chronique et seulement 12 % étaient restés en bonne santé. Avec un suivi suffisamment long et attentif, il apparaît que la presque totalité des patients traités pour dépression majeure ne guérissent pas, ou présentent une rechute.

Néanmoins, il y a beaucoup d’arguments en faveur de l’administration de traitements appropriés pour la dépression, pour des motifs tant personnels que socio-économiques. Pourtant, jusqu’à présent, l’insuffisance de traitement reste très fréquent. Sur les 17 % de personnes souffrant de dépression majeure identifiées au cours d’une enquête européenne portant sur 78 000 adultes, 69 % ne recevaient aucun traitement médical, 43 % n’avaient même jamais consulté un médecin, et moins de 8 % recevaient un antidépresseur. En outre, le traitement antidépresseur administré est souvent suboptimal : une enquête portant sur un million de patients...
de soins primaires a montré que 89 % d’entre eux recevaient une dose subthérapeutique d’an-
tidépresseur tricyclique (ATC)
. Heureusement, le sous-dosage est devenu moins fréquent avec
les nouveaux antidépresseurs, notamment les inhibiteurs sélectifs de la recapture de la séro-
tonine (ISRS), qui sont uniquement commercialisés à des doses thérapeutiques.

La mauvaise réponse thérapeutique est fréquemment due à une mauvaise observance du
traitement par le patient : 30 % des patients de soins primaires ne se sont jamais fait délivrer
leur première prescription, tandis que 25 à 33 % de patients supplémentaires interrompent leur
traitement au cours du premier mois, et 62 % n’en informent pas leur médecin. Par conséquent,
la durée du traitement dans 55 à 63 % des cas est inférieure à la recommandation minimale
établie de six mois après la rémission
. Cependant, même dans des études bien conduites portant
sur différentes classes d’antidépresseurs administrés pendant les 6 à 8 semaines généralement
considérées comme suffisantes pour démontrer une différence entre un médicament actif et un
placebo, les taux d’absence de réponse thérapeutique se situent en moyenne entre 30 et 40 %.

Le développement des antidépresseurs

Le mécanisme d’action invoqué pour les des inhibiteurs de la monoamine oxydase (IMAO) et des
ATC était le blocage de la recapture des neurotransmetteurs monoaminergiques, la noradré-
naline et la sérotonine (5-HT), augmentant ainsi leur disponibilité dans la fente synaptique. La
dépression était supposée provenir de concentrations subnormales de neurotransmetteurs. Bien
que simpliste et incomplète, cette théorie a fourni une base fructueuse pour le développement
de la plupart des antidépresseurs découverts par la suite. Les recherches se sont concentrées
sur la découverte de composés présentant une sélectivité supérieure pour l’une ou l’autre des
monoamines, diminuant ainsi les effets indésirables. La maprotiline et la réboxétine sont des
exemples d’inhibiteurs sélectifs de la recapture de la noradrénaline (ISRN). Mais les efforts les
plus importants se sont portés sur le développement des ISRS, et ont culminé avec la mise sur
le marché de la fluoxétine, la paroxétine, la fluvoxamine, la sertraline, le citalopram et l’esci-
talopram qui dominent aujourd’hui le marché des antidépresseurs.

Il a été découvert que plusieurs ATC agissaient sur les récepteurs 5-HT₂ : l’amitriptyline
bloque à la fois la recapture de la 5-HT₂ et exerce une action antagoniste sur les récepteurs
5-HT₂. Ce phénomène a inspiré le développement d’antagonistes des récepteurs 5-HT₂ comme
la trazodoné, suivie par des composés encore plus sélectifs agissant sur des sous-types de récep-
teurs 5-HT₂, comme l’agonométatine, un antagoniste des récepteurs 5-HT₂C et la mélatonine, un
agoniste des récepteurs de type M₁ et M₂, et la miansérate et la mirtazapine, qui sont des anti-
tagones des récepteurs 5-HT₂A et 5-HT₂C, ainsi que des antagonistes α₂ et des antagonistes des
récepteurs 5-HT₁A et 5-HT₃.

Supériorité de certains antidépresseurs particuliers

Les essais cliniques sur les antidépresseurs n’ont pas permis de démontrer une réponse constam-
tement supérieure à un traitement actif par rapport à un placebo
. Cela est dû, quelle que soit
l’(in)efficacité des antidépresseurs eux-mêmes, au schéma et au déroulement inappropriés des
études, et à certains obstacles théoriques et pratiques majeurs. L’une des insuffisances impor-
tantes a été une puissance inadéquate, tandis qu’un certain nombre d’études « sans succès »
n’ont jamais été publiées. Des études de petite taille démontrant une efficacité significative ont
souvent été limitées à des patients hospitalisés souffrant de dépression sévère, tandis que le pas-
sage à des études plus réalistes sur la population de ville a conduit au recrutement d’un grand
nombre de patients souffrant de dépression légère pour lesquels une différence entre le médi-
cament actif et le placebo a été difficile à mettre en évidence. Même les critères diagnostiques du
trouble dépressif majeur se sont avérés inadéquats, en particulier en ce qui concerne la durée
de la maladie. Tandis que les critères du DSM IV [Diagnostic and Statistical Manual of Mental
Disorders, 4th Edition] ne demandent que deux semaines, une durée compatible avec un trouble
spontanément résolutif, les investigateurs ont depuis longtemps augmenté la durée minimale
d’un épisode à un mois pour justifier d’une inclusion dans ce type d’études.

La différence entre les médicaments est encore plus difficile à démontrer. Les ISRS peuvent
être plus sûrs et mieux tolérés que les ATC, mais ils sont apparus significativement moins effi-
caces que le traitement classique par la clomipramine dans une étude importante
. Malgré ses
faiblesses méthodologiques, cette étude a suggéré que la sélectivité pour le système de la sé-
rotonine pouvait ne pas s’avérer universellement bénéfique. Une conclusion plausible a été que
les antidépresseurs sélectifs ne pourraient être efficaces que chez les patients présentant un dé-
ficit significatif en monoamines, une théorie corroborée par des comptes rendus de plusieurs
études ultérieures selon lesquelles des ISRN, comme la venlafaxine, se sont avérés plus efficaces que les ISRS\textsuperscript{10}, qui ont eux-mêmes été significativement plus efficaces que le placebo. Cependant, cette conclusion n’a pas permis d’établir une conviction consensuelle, même avec le soutien d’une méta-analyse, à cause d’un ensemble d’insuffisances méthodologiques.

Une rare occasion pour effectuer une méta-analyse médicamenteuse valide a été fournie par les études groupées sur deux ISRS, l’escitalopram et le citalopram, dans la mesure où elles ont toutes deux été de la même durée de 8 semaines et ont utilisé l’échelle d’évaluation de la dépression de Montgomery & Asberg (Montgomery and Asberg Depression Rating Scale, MADRS) : plusieurs méta-analyses effectuées pour un certain nombre d’affections sont arrivées à la conclusion générale que l’escitalopram était la substance la plus efficace\textsuperscript{11}.

Déclenchement précoce de la réponse
L’un des inconvénients bien connus des antidépresseurs est qu’une différence significative avec le placebo ne peut être mise en évidence de façon fiable qu’environ six semaines après le début du traitement. Ce délai est potentiellement dangereux, car les risques de suicide sont élevés dans la période précoce du traitement lorsque la sévérité est maximale. L’absence d’effet positif rapide décourage également l’observance thérapeutique. C’est la raison pour laquelle un déclenchement plus précoce de l’effet thérapeutique serait bienvenu. Malheureusement, pratiquement aucune étude n’a analysé cet aspect sur les antidépresseurs examinés individuellement. Une analyse rétrospective d’études contrôlées par placebo portant sur la venlafaxine indique simplement qu’une réponse est observée avant deux semaines avec une augmentation précoce et rapide à des doses élevées, tandis que des études comparatives ont suggéré que l’escitalopram induisait une réponse plus rapide que le citalopram\textsuperscript{12}.

Efficacité sur des symptômes spécifiques
Certains symptômes s’améliorent plus rapidement avec un antidépresseur qu’avec un autre.

\bf{Sommeil}
Les antidépresseurs présentant une activité antihistaminergique, par exemple l’amitriptyline et la mirtazapine, améliorent le sommeil précocement au cours du traitement, mais au prix d’une altération de la vigilance diurne et de troubles de la concentration. Les antagonistes des récepteurs 5-HT\textsubscript{2}, par exemple la néfazodone, améliorent le sommeil sans inconvenients de ce type, de même que l’agomélatine, un agoniste mélatoninergique et un antagoniste sélectif des récepteurs 5-HT\textsubscript{2c}.

\bf{Symptômes douloureux et somatiques}
Les ISRN pourraient être plus efficaces pour soulager les syndromes douloureux. Ainsi, la venlafaxine a été supérieure à un placebo dans la neuropathie diabétique. En fait, les ISRN pourraient être plus efficaces d’une manière générale sur les symptômes somatiques de dépression\textsuperscript{13}. Bien qu’il ne s’agisse pas des symptômes centraux de ce trouble, ils peuvent expliquer l’avantage apparent des ISRN sur les ISRS, en particulier lorsque la rémission est estimée par l’échelle d’évaluation de la dépression de Hamilton (Hamilton Depression Rating Scale) avec sa surreprésentation des symptômes somatiques. L’avantage peut apparaître de façon moins nette en utilisant une échelle des symptômes centraux, comme l’échelle MADRS.

\bf{Interruption du médicament}
Des études antérieures sur les ATC ont établi que l’interruption brutale du traitement provoquait un syndrome de sevrage se manifestant par des nausées, des vomissements, des maux de tête, des vertiges, des frissons, une faiblesse et des douleurs musculosquelettiques chez certains patients. Les symptômes étaient transitoires, atteignant une intensité maximale au cours de la première semaine puis ont décruant par la suite, interrompant rarement avec le fonctionnement.

Un syndrome de sevrage a également été observé avec des ISRS, que le retrait ait été progressif ou brutal. Son apparition dépend de la demi-vie du composé considéré et de ses métabolites actifs. Avec la fluoxétine, par exemple, le syndrome de sevrage peut apparaître après quatre semaines, tandis qu’avec la paroxétine, son intensité est maximale au cours de la première semaine. Les résultats montrent de façon constante que le syndrome était plus fréquent avec la paroxétine qu’avec la sertraline ou la fluoxétine\textsuperscript{14}, et qu’il se manifestait par une insomnie, une augmentation des rêves, des douleurs musculaires, des vertiges, des frissons, une rhinorrhée, des nausées et une diarrhée.
Le seul antidépresseur qui n’est pas associé à un syndrome de sevrage est l’agomélatine. Il s’agit d’un avantage important dans la mesure où de nombreux patients recevant des antidépresseurs sont inconstants et oublient de prendre leur médicament pendant quelques jours au cours du traitement, et seraient, par conséquent, susceptibles de présenter des symptômes de sevrage.

Suicide
Le risque de suicide est maximal au début du traitement, et il est lié à la sévérité de la maladie. Le meilleur facteur prédicatif est constitué par des antécédents de tentative de suicide, bien qu’ils soient absents dans plus de la moitié des cas de suicides. Un suivi à long terme a montré que les antidépresseurs réduisaient le risque de suicide d’un facteur 3 dans la dépression majeure unipolaire, une statistique confirmée par des études épidémiologiques effectuées chez des adultes suédois et des adolescents américains.

Dans la mesure où il s’agit d’un événement rare dans les études cliniques, le risque de suicide lié à un médicament individuel ne peut pas être évalué, même à partir des larges ensembles de données nécessaires aux demandes d’autorisation de mise sur le marché remis aux autorités réglementaires. Cependant, une récente méta-analyse effectuée sur des données portant sur plus de 40 000 patients soumises aux autorités sanitaires a montré une réduction non significative du nombre de suicides avec les ISRS par rapport à un placebo. Une comparaison décisive nécessiterait l’inclusion de millions de patients dans des études contrôlées par placebo.

Les résultats concernant les pensées suicidaires enregistrées comme événement indésirable ont été similaires. Ces pensées étant mesurées en utilisant les principales échelles d’évaluation de la sévérité de la dépression, ces dernières constituent la meilleure base pour l’évaluation. Plusieurs antidépresseurs, notamment l’imipramine, la paroxétine et l’escitalopram, sont significativement plus efficaces que le placebo dans la protection contre l’émergence des pensées suicidaires.

Sécurité d’emploi
Les effets indésirables constituent une cause majeure de non observance du traitement. Les ATC présentent un inconvénient particulier à cet égard, dans la mesure où ils exercent une large variété d’actions pharmacologiques outre leur activité sur les systèmes de la noradrénaline et de la sérotonine. Leurs effets sur les récepteurs muscariniques entraînent des réactions anticholinergiques comme une sécheresse buccale, une vision trouble, une constipation, un retard à la miction et des déficits cognitifs, tandis que les effets sur les récepteurs α1-adrénergiques sont responsables de vertiges et d’hypotension, qui représentent un problème particulier chez les personnes âgées à cause des chutes et des fractures. Les effets histaminiques provoquent une séduction et des troubles de la concentration. Au total, il en résulte une mauvaise tolérance et un traitement aléatoire.

L’absence d’effets similaires sur ces récepteurs fait que les ISRS devraient être mieux tolérés, et s’accompagner d’un moindre nombre d’interruptions prématurées du traitement. Cependant, les ISRS exercent plusieurs effets indésirables sérotoninergiques caractéristiques ; ils entraînent des effets gastro-intestinaux indésirables, par exemple des nausées et vomissements. Certains ISRS, par exemple la fluoxétine, provoquent une augmentation de l’agitation et de la nervosité, en particulier au début du traitement. Leurs effets indésirables sexuels comprennent une anorgasmie chez la femme et un retard à l’éjaculation chez l’homme. Il semble que les nausées puissent être partiellement tolérées, ce qui est moins le cas pour les effets indésirables sexuels.

Certains antidépresseurs ont montré qu’ils provoquaient moins d’effets indésirables sexuels, par exemple la néfazodone, ce qui pourrait être lié à ses propriétés antagonistes des récepteurs 5-HT2C. Le buproprion présente un avantage similaire par rapport aux ISRS, bien qu’il ne soit pas commercialisé comme antidépresseur en Europe. L’agomélatine semble relativement exempte d’effets indésirables sexuels : une étude spécifique a montré sa supériorité significative par rapport à la venlafaxine chez des patients en rémission. Il existe également des éléments montrant que la mirtazapine, un antagoniste des récepteurs 5-HT2, n’avait pratiquement aucune association avec un dysfonctionnement sexuel.

Les ISRN sont associés à tous les effets indésirables des ISRS, auxquels s’ajoutent certains effets liés à la noradrénaline, notamment la sécheresse buccale, la constipation et l’augmentation de la fréquence cardiaque. Par conséquent, des doses élevées de venlafaxine sont susceptibles de provoquer un excès d’effets sérotoninergiques. La venlafaxine est également associée...
à une augmentation de la pression artérielle et du cholestérol, ce qui doit être pris en compte lors de la prescription. La duloxétine est autorisée à faible dose précisément pour réduire les risques d’effets indésirables excessifs. La venlafaxine et la duloxétine semblent être moins bien tolérées que les ISRS.

Conclusion
La dépression est un trouble fréquent et invalidant qui impose un lourd fardeau aux patients, à leurs parents et amis, et à la société dans son ensemble. Elle est également dangereuse, dans la mesure où elle est associée à une augmentation de la morbidité et de la mortalité, y compris liées au suicide. La dépression raccourcit la vie en moyenne de 10 ans. D’une manière générale, les traitements disponibles sont efficaces, mais leur utilisation est compromise par une mauvaise tolérance et une observance insuffisante. Seul un très petit nombre d’individus déprimés reçoivent un traitement, et parmi ceux-ci, il est rare qu’il soit prescrit à une posologie adéquate et pour une durée suffisante pour assurer une réponse complète. Il existe un besoin manifeste pour des traitements plus efficaces, plus rapidement efficaces et mieux tolérés. Ils permettraient de réduire le nombre de patients présentant une réponse insuffisante ou inadéquate, et laisseraient moins de patients souffrir d’une dépression réfractaire. La mauvaise observance et l’interruption prématurée du traitement réduisent actuellement les chances de guérison. Des antidépresseurs dont le déclenchement d’action serait plus rapide permettraient d’augmenter le nombre de patients déprimés bénéficiant d’une rémission complète.
Chronobiological strategies for unmet needs in the treatment of depression

by A. Wirz-Justice, Switzerland

Chronobiological strategies may provide an effective means of addressing some of the unmet needs in the treatment of depression, such as shortening the latency of onset of antidepressant action, combating residual symptoms, and preventing relapse in the long term. Light is the treatment of choice for winter depression (or seasonal affective disorder, SAD). Light therapy given as an adjuvant to medication in major nonseasonal depression, as well as in chronic and therapy-resistant depression, speeds up and potentiates clinical response. Light is also efficacious in bipolar depression; in these patients “dark therapy” (long nights) can diminish manic symptoms and stop rapid cycling. Total or partial sleep deprivation in the second half of the night (better known as “wake therapy”) induces marked improvement the following day. This amelioration can be maintained with concomitant treatment with antidepressants, lithium, light therapy, sleep phase advance, or combinations thereof. Careful control of the light-dark cycle and of the timing of mealtimes, activity, and sleep may appear to be old-fashioned methods (“daily structures”) belonging to a long obsolete custodial psychiatry. However, these apparently simple methods gain new validation when reconsidered within the framework of modern chronobiology, since when appropriately timed, application of “zeitgebers” can aid treatment of affective disorders.


Keywords: major depression; circadian rhythm; sleep deprivation; light therapy; melatonin

Why are we interested in biological rhythms?

One of the most striking clinical phenomena in affective disorders is the periodicity of recurrence—ranging from seasonal, as in winter depression, to rapid cycling, which can be as short as 48 hours (reviewed in 5). Other periodic phenomena are found at the symptom level: diurnal variation of mood, manic phases, and the timing of sleep.

Selective abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Definition</th>
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<tr>
<td>5-HT</td>
<td>serotonin</td>
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<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
<td>serotonin receptor (subtype 2C)</td>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<tr>
<td>PVN</td>
<td>paraventricular nucleus</td>
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<tr>
<td>SAD</td>
<td>seasonal affective disorder</td>
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<tr>
<td>SCN</td>
<td>suprachiasmatic nucleus</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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The field of chronobiology studies 24-hour biological clocks (the circadian system) and their synchronizers (“zeitgebers”) such as light, the pineal hormone melatonin, food, activity, as well as the factors regulating sleep. Light therapy has arisen out of this basic research in circadian rhythms, whereas, in contrast, sleep deprivation (“wake therapy”) was established by astutely following up clinical observations. Chronotherapeutics can be defined as translating basic chronobiology research into valid treatments. The term is broad, and the treatments subsumed under this heading will grow as the field grows, and are of course not limited to affective disorders (there is an important body of evidence, for example, that the correct timing of cancer treatments augments survival and diminishes the often potent side effects).

The theme of meeting unmet needs in the treatment of depression is important and timely. The onset of action of antidepressants is still not rapid enough, a proportion of patients do not respond, others have residual symptoms that predict relapse. Although medication based on classic neurotransmitter systems is still a prime focus, drug targets other than monoamines are under intensive investigation. Strategies promoting adjuvant therapy are on the increase, whether they encompass combination with other medications (eg, addition of pindolol, of thyroid hormone) or psychological interventions (eg, cognitive behavioral therapy). Mainstream psychiatry is becoming more and more eclectic, implementing a variety of approaches to help the individual patients. The question to be discussed here is focused on why not also combine the chronobiological strategies of light therapy and/or wake therapy with psychopharmacological medication? Light therapy has undergone widespread controlled randomized clinical trials, and wake therapy has been so widely studied over decades that the efficacy data are strong. These nonpharmaceutical, biologically based therapies are not only powerful adjuvants, but also antidepressants in their own right.
early morning awakening, and sleep disturbances. Abundant research has documented abnormal circadian rhythms in biochemistry, neuroendocrine function, physiology, and behavior, often linked to changes in affective state. These have been reviewed in detail elsewhere; the findings are not homogeneous, even though a certain pattern appears characteristic of depression—there is increased variability in day-to-day rhythms, decreased circadian amplitude, and circadian phase that is either early (advanced) or late (delayed). Bipolar disorder seems to be most clearly linked to abnormal or changing circadian rhythm phase. In addition, alterations in the sleep EEG in depression, although neither pathognomonic nor specific, display recognizable patterns of disturbance.

**Principles of circadian timing and sleep regulation**

The biological timing system is schematically described in Figure 1. Circadian oscillators are found in every organ and every cell—the so-called “peripheral clocks.” A master pacemaker or biological clock in the suprachiasmatic nuclei (SCN) coordinates these circadian rhythms in brain and body. The SCN is synchronized to the external light-dark cycle primarily by retinal light input. A specialized (“nonvisual”) retinohypothalamic tract provides direct neuronal connection to the SCN from novel photoreceptors in the retina. A multisynaptic pathway to the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal “circadian photoreceptors” in the retina. A multisynaptic pathway to the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal “circadian photoreceptors” in the retina. A multisynaptic pathway to the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light.

**Mood is dependent on both time of day and time awake**

This parsimonious two-process model has been able to explain much of the physiology of sleep as well as of aberrant sleep-wake cycle behavior. Protocols developed to analyze the contributions of circadian phase vs the sleep homeostat have provided fascinating information not only about sleepiness—as might be expected—but also that mood is similarly regulated by the two processes. This is shown very clearly in the “forced desynchrony” protocol carried out in healthy subjects. The circadian component of mood follows the circadian rhythm of core body temperature rather closely. We wake up in not too good a mood, but this improves throughout the day to reach a maximum in the evening, and then mood declines during the night. The wake-dependent component reveals that we are quite cheery after a good night’s sleep when sleep pressure is low, but that thereafter mood declines monotonically with time awake. If the temporal alignment between the sleep-wake cycle and the circadian pacemaker affects self-assessment of mood in healthy subjects, it might be expected that this is even more important for patients with depression. The phenomenon of diurnal mood variation as a characteristic of depressive state may indeed arise from phase relationships gone awry.

Diurnal mood variation can be manipulated by shifting or depriving sleep. The improvement after a night’s wake therapy usually begins in the second half of the night or the next day, suggesting that staying awake prevents the nocturnal plunge in mood. Furthermore, a phase advance of sleep timing has been able to induce a day-by-day change in diurnal mood patterns over many weeks—evidence for the profound effect of shifting phase relationships on mood (a more severe form of jet lag). Similar day-by-day changes in diurnal mood patterns have been found in a “forced desynchrony” experiment carried out in major seasonal depression.

**Shifting rhythms or sleep can be therapeutic**

The above model helps to understand the change of clinical state with time of day and after manipulations of sleep. The clinical findings, however, are the important point to be made—extending wakefulness is antidepressant. Wake therapy has been well

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**Figure 1.** Schematic representation of the circadian timing system. Light (太阳) is the major zeitgeber reaching the biological clock in the SCN via specialized “circadian photoreceptors” in the retina (视网膜). A multisynaptic pathway to the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light. Melatonin feeds back on the pineal gland via the paraventricular nucleus (PVN) drives the nocturnal synthesis of melatonin and its suppression by light.
established as a rapid treatment for depression for over 30 years, the response being particularly high in those patients who report daily mood swings. Modified protocols have been developed, such as wake therapy in the second half of the night, or phase advance of the sleep-wake cycle. These two modifications emphasize the circadian factor—it being important to remain awake at a particular time in order to prevent mood decline.

The main reason for the lack of enthusiasm for wake therapy as a treatment in everyday practice is the equally rapid relapse following recovery sleep. A number of groups have taken up the challenge of searching for methods to prevent this: do not give up wake therapy as a treatment just because its effects don’t last long enough! In bipolar patients, the combination with lithium appears to maintain antidepressant response. A number of different medications have been tried; in particular, the use of SSRIs or light is recommended following one to three episodes of wake therapy.

How are circadian rhythms related to depression?

The basic question of how circadian rhythms are related to depression has not yet been answered. Genetic vulnerability and stress influence circadian rhythms and sleep patterns, leading to many of the symptoms characteristic of affective disorders. Circadian and seasonal rhythms involve the same neurotransmitters postulated to be important for depression—so that changes in one system have repercussions on the other. For example, it is known that serotonin concentrations are highest in the SCN. The SCN also expresses high levels of melatonin receptors, and exogenous melatonin is known to be able to influence the phase and the period of sleep disorders (such as advanced or delayed sleep phase syndrome) without effects on mood. Serotoninergic abnormalities alone lead to other serotonin-related illnesses (eg, obsessive compulsive disorder) again, without the mood disorder.

A digression on seasonality

Humans retain their capacity to undergo seasonal responses, even though their extent has declined in the last century since the invention of artificial light and the use of central heating and air conditioning to control environmental temperature. This is clearly seen in the seasonality of birth (conception) rates, that had a high spring peak in the 16th century, but declined to very low amplitude in the 20th century, with a shift to an autumn peak. Psychiatrists have long remarked on seasonality in their patients’ symptoms, for example Esquirol, who noted that the peak admission rates to the Salpêtrière hospital occurred in spring. What is not usually recognized, is that not only depressive symptoms, but even response to placebo is seasonally modulated. The 10-day response rate to placebo in double-blind controlled trials of various antidepressants carried out at the New York State Psychiatric Institute was analyzed according to time of year (Figure 4, page 226). Three times higher response rates occurred in summer than in winter. In conclusion, many aspects of behavior, physiology, and neuroendocrine abnormalities alone lead to other serotonin-related illnesses (eg, obsessive compulsive disorder) again, without the mood disorder.
Unmet Needs in the Treatment of Depression

As for the seasons, the annals of psychiatry abound with evidence that affective state can be modulated by exposure to environmental light or darkness. The diagnosis of seasonal affective disorder (SAD) and the development of light therapy was based on neurobiological models of mammalian seasonality—the first treatment in psychiatry to be grounded in basic research. Although light therapy was initially propagated by Kripke for nonseasonal depression, initial studies were too short in duration to provide the convincing results that a single week of light therapy can now achieve in SAD: it is only now, 20 years on, that controlled long-term studies of light at last have been and are being carried out in nonseasonal major depression, with extremely promising results. For example, the need for efficacious treatment of depression during pregnancy without side effects on the fetus has led to trials of monotherapy with light. Double-blind placebo-controlled studies have now shown that light therapy combined with an SSRI leads to more rapid (within 1 week) and more profound (by ca 30%) improvement in patients with nonseasonal major depression. Recently, a study of light treatment in chronic depression (of greater than 2 years duration) yielded impressive results in this often treatment-resistant group. Thus, a new generation of clinical trials supports the therapeutic efficacy of light, alone or in combination with medication, for a variety of psychiatric disorders, and it is to be hoped that more will follow.

“More darkness” is a correlate of the above: pilot studies suggest that the simple measure of promoting long nights (more rest, more sleep, no light) can stop rapid cycling in bipolar patients or diminish manic symptoms—intriguing findings that require replication.

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Can chronotherapeutics provide new drugs as well?

Not only are the described chronotherapeutic approaches efficacious antidepressants in themselves, but they also offer new models for pharmaceutical research. Is part of the usefulness of light due to its zeitgeber function of stabilizing phase? Is part of its efficacy due to serotonergic mechanisms? Given that the antidepressant properties of selective serotonin (5-HT) reuptake–inhibiting drugs are considered to be related to the 5-HT2C receptor subtype, it is interesting that 5-HT2C receptor agonists in the rat SCN mimic the effects of light. Serotonergic drugs and melatonin improve entrainment. In this respect, the pharmacological profile of agomelatine fits the above model, as it is a melatonin receptor type 1 and 2 (MT1 and MT2) agonist with 5-HT2C properties. Melatonin itself has no antidepressant characteristics.

In summary, circadian rhythm and sleep research have led to nonpharmacological therapies of depression (light therapy, wake therapy) that can be—and should be—used in everyday practice. The rationale for attempting to resynchronize disturbed phase relationships between the clock and sleep is the concomitant improvement in mood. Chronobiological concepts emphasize the importance of zeitgebers and provide psychopharmacology with a novel approach for developing “chronobiotic” drugs.

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**Stratégies chronobiologiques pour les besoins insatisfaits dans le traitement de la dépression**

Les stratégies chronobiologiques peuvent représenter un moyen efficace pour faire face à certains besoins insatisfaits dans le traitement de la dépression. Ce sont : le raccourcissement du temps de latence qui précède l’apparition de l’effet antidépresseur, la lutte contre les symptômes résiduels et la prévention de la rechute à long terme. La lumière est le traitement de choix pour la dépression hivernale (ou trouble affectif saisonnier, TAS). La luminotherapie, comme adjuvant au traitement dans la dépression non saisonnière majeure comme dans la dépression chronique et résistante au traitement, accélère et potentialise la réponse au traitement. La lumière est aussi efficace dans la dépression bipolaire ; chez ces patients présentant ce trouble, le « traitement par l’obscurité » (nuits longues) peut diminuer les symptômes maniaques et arrêter les cycles rapides. La privation totale ou partielle de sommeil dans la seconde partie de la nuit (mieux connue sous le nom de « traitement par l’éveil ») induit une amélioration marquée le jour suivant. Cette amélioration peut être maintenue avec des traitements concomitants par les antidépresseurs, le lithium, la luminotherapie, l’avance de phase de sommeil ou l’association de plusieurs de ces mesures. Un contrôle soigneux du cycle jour-nuit et de l’heure des repas, de l’activité et du sommeil peut apparaître comme une méthode démocédée (mise en place de « structures journalières ») appartenant à une obsession psychiatrie d’institutionnalisation. Cependant, ces méthodes apparemment simples retrouvent une nouvelle légitimation quand on les considère à l’intérieur du cadre de la chronobiologie moderne, puisque l’utilisation bien réglée de « synchroniseurs », ou « zeitgeber » peut améliorer le traitement des troubles affectifs.
New perspectives in the pathophysiology and treatment of affective disorders: the role of melatonin and serotonin

by M. Hamon, P.-A. Boyer, and E. Mocaër, France

For almost 50 years, since the empirical discovery of the antidepressant properties of the monoamine oxidase inhibitors (MAOIs) and tricyclics, the “monoamine hypothesis,” according to which depression involves imbalances in serotonergic, noradrenergic, and possibly dopaminergic function, has held sway over the concepts and theories put forward to explain the pathophysiology of depression. More recently, however, other approaches to the understanding of the central mechanisms of antidepressant drugs have been explored, and have revealed the existence of important neurobiological changes in response to chronic treatment with these drugs.

Keywords: depression; monoamine hypothesis; neurotransmitter; circadian rhythm; melatonin; serotonin; agomelatine

SELECTED ABBREVIATIONS AND ACRONYMS

5-HT 5-hydroxytryptamine (serotonin)
BDNF brain-derived neurotrophic factor
CREB cyclic (adenosine monophosphate) response element binding (protein)
CRF corticotropin-releasing factor
ECT electroconvulsive therapy
HPA hypothalamo-pituitary-adrenocortical (axis)
MAOI monoamine oxidase inhibitor
MT melatonin (receptor)
NE norepinephrine
NK neurokinin (receptor)
NMDA N-methyl-D-aspartate
SCN suprachiasmatic nuclei
SNRI selective norepinephrine reuptake inhibitor
SSRI selective serotonin reuptake inhibitor
The “monoamine hypothesis”

The monoaminergic pathways play a crucial role in the control of mood and cognition, as well as of endocrine secretions and chronobiotic rhythms, all of which are disrupted in depressive states. It was thus very logical to postulate a perturbation of monoaminergic transmission in the etiology of depressive disorders. This has been consistently borne out by the findings from monoamine depletion studies in patients, which confirmed the importance of functionally competent monoaminergic pathways for combating depressive states, as well as by the proven clinical efficacy of available treatments of depression in restoring the compromised activity of the corticolimbic monoaminergic pathways. Drugs facilitating neurotransmission mediated by monoamine neurotransmitters, especially serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE), generally exert a positive influence on mood. By blocking the key enzyme in the catalytic pathways of both 5-HT and NE, MAOIs increase the concentrations of these neurotransmitters in the synaptic cleft at serotonergic and noradrenergic receptor level. In contrast, tricyclic antidepressants, which have also been shown to increase the concentrations of monoamines at the receptor level, act via blockade of the reuptake process of these neurotransmitters from the extracellular space. Several key observations demonstrated that the resulting increase in extracellular concentrations of both 5-HT and NE entirely accounted for the antidepressant effects of tricyclics. Drugs were therefore designed to mimic the inhibitory effects of tricyclics via specific action on the 5-HT transporter (selective serotonin reuptake inhibitors, or SSRIs) or the NE transporter (selective norepinephrine reuptake inhibitors, or SNRIs), or both. These drugs, which increased extracellular concentrations of both 5-HT, NE, or both, were shown to exert potent antidepressant actions, and are currently the drugs most widely used in the treatment of major affective disorders.

Second-generation antidepressants are safer than first-generation agents because SSRIs and SNRIs do not generally interact with the various receptor types (histaminergic, cholinergic, α-adrenergic, etc) on which tricyclic antidepressants act as antagonists. Nevertheless, second-generation antidepressants offer little advantage in terms of efficacy, and there remains a need for antidepressants that do not require several weeks of administration prior to full expression of clinical efficacy. Furthermore, there is also a need to reduce undesirable side effects, such as sexual dysfunction, insomnia, and weight gain, which make the use of at least some of these drugs rather delicate, since they compromise patient compliance and reduce drug efficacy.

It is now well recognized that synaptic facilitation and augmentation of the levels and effects of NE and 5-HT are only part of the explanation of the action of antidepressants. The pure “monoamine hypothesis” is too restrictive, and depression cannot be simplistically ascribed to the dysfunction of monoaminergic systems only. Rather, it reflects a complex disruption not only of monoaminergic pathways, but of other pathways as well. In particular, the “monoamine hypothesis” fails to explain the 3 to 4 weeks’ delay in the therapeutic efficacy of MAOIs, tricyclics, SSRIs, and SNRIs. The temporal mismatch between the rapid elevations in extracellular levels of monoamines induced by antidepressant agents, and their slow onset of therapeutic action reflects the initiation of adaptive mechanisms involving secondary or even tertiary changes in receptor density, intracellular signaling, synaptic transmission, neuronal architecture, and neurogenesis.

The aforementioned adaptive changes in monoaminergic receptors were initially claimed to reflect therapeutically relevant neurobiological changes induced by long-term antidepressant treatment. Downregulation of cortical β1-adrenergic and 5-HT2A serotoninergic receptors was long considered as a biological marker of effective antidepressant therapy with tricyclics. This was confirmed by evidence of postmortem upregulation of these receptors in depressed patients having committed suicide. However, other findings indicated that electroconvulsive therapy (ECT) was associated with upregulation of cortical 5-HT2A receptors, and that chronic treatment with most SSRI antidepressants was unable to downregulate cortical β1-receptors. Furthermore, functional changes after chronic administration of at least some classes of antidepressants were evidenced for other receptor types, especially 5-HT1A receptors. In particular, there have been consistent reports of desensitization of 5-HT1A autoreceptors in the dorsal raphe nucleus, with no changes in hippocampal 5-HT1A heteroreceptors, after chronic treatment with MAOIs, SSRIs, or NK1 receptor antagonists as well as after transcranial magnetic stimulation and ECT. In contrast, hypersensitivity of hippocampal 5-HT1A receptors with no changes in 5-HT1A autoreceptors has been found to occur in response to chronic administration of tricyclic antidepressants. Nevertheless, the “monoamine hypothesis” did not entirely account for the action of the antidepressants, and researchers began looking for other possible mechanisms of action.

Other approaches to the understanding of the mechanism of action of antidepressant drugs

An important consideration was that of the possible involvement of the hypothalamo-pituitary-adrenocortical (HPA) stress axis: upregulation of glucocorticoid receptors, notably in the hippocampus, was evidenced with various antidepressant drugs following long-term administration. This change is very probably linked to the therapeutic action of these drugs, since it contributes to restoring normal functioning of the depression-associated deficient negative feedback control of the HPA axis, thereby decreasing excessive cortisol secretion back to normal in depressive patients. High levels of glucocorticoids are generally associated with a negative influence upon mood, as well as deleterious structural changes in the hippocampus, perhaps via reduced brain-derived neurotrophic factor (BDNF).
Neurokinin type 1 (NK₁) receptor antagonists have been claimed to exert antidepressant activity independent of monoamines in relevant animal paradigms as well as in humans, by inhibiting the action of substance P, a tachykinin neuropeptide that is localized in brain regions involved in the control of stress and emotion.²⁶

However, there is a possibility that both CRF and NK₁ antagonists may also act, indirectly, through monoaminergic mechanisms. Indeed, tachykinin NK₁ receptor antagonists activate noradrenergic and dopaminergic pathways innervating the hippocampus and the frontal cortex, and long-term treatments with these antagonists produce the same adaptive changes in 5-HT neurotransmission as those observed after chronic treatment with MAOIs or SSRIs.¹⁷ In addition, recent investigations clearly demonstrated that CRF antagonists indirectly enhanced the activity of serotonergic pathways although they do not, unlike tachykinin NK₁ receptor antagonists, activate dopaminergic input to the cortex and may inhibit the activity of noradrenergic neurons.¹⁹,²⁰

Levels of BDNF are usually found to be increased in response to long-term antidepressant drug treatment. This is probably related, at least in part, to the negative influence of glucocorticoids on BDNF synthesis.²¹,²² Actually, chronic intracerebroventricular infusion of BDNF exerts antidepressant-like effects via activation of its receptors, TrkB.²³ Findings also suggest that progressive induction of BDNF and the resulting enhancement of neurogenesis are causaly related to the onset of antidepressant activity.²⁴ Experimental studies on stress and antidepressant treatments have recently implicated neurogenesis in the etiology of major depressive disorders.²⁵,²⁶ So far, all chronic treatments aimed at alleviating depression, including ECT, have been shown to stimulate the proliferation of progenitor cells at the origin of granular neurons in the dentate gyrus of the hippocampus.²⁷ The precise functional significance of these newly generated neurons in the pathophysiology of mood disorders is still disputed, but a recent study by Santarelli et al.²⁸ supports the idea that granule cell proliferation is directly related to the therapeutic action of antidepressant drugs, since suppression of this process by x-ray exposure resulted in loss of the antidepressant-related behavorial effects. In addition, the antidepressants have been found to modulate the expression of various factors involved in cell survival and growth, such as cyclic adenosine monophosphate response element binding protein (CREB), bcl-2, and mitogen-activated protein (MAP) kinases.²⁹,³⁰

Finally, the complex pattern of mutual interactions between glutamatergic and monoaminergic networks plays a crucial role in the control of mood and cognition.¹¹,¹² Excessive corticolimbic glutaamate release upon chronic exposure to stress may contribute to the development of depressive states.³³ In this regard, most studies have focused on the role of detrimental N-methyl-d-aspartate receptor (NMDA)–mediated alterations in the structure of hippocampal neurons.³⁴,³⁵ A number of antidepressants, as well as ECT, exert regulatory actions on the NMDA receptor complex, and some NMDA receptor antagonists have antidepressant-like properties.³⁶

### Depression and abnormal circadian rhythms

In humans, the circadian pacemaker, or biological clock, is the site of the generation and entrainment of circadian rhythms. It is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The great majority of physiological, metabolic, and behavioral functions are controlled by the circadian pacemaker and are often used as circadian phase markers. The circadian pacemaker is sensitive to light throughout the 24-h cycle and to the phase-shifting effects of various chemical and pharmacological components, including melatonin, which acts on the circadian clock through melatonin receptors located in the SCN.³⁵

A wide range of affective disorders, including unipolar and bipolar depression, mania, seasonal affective disorder, and premenstrual dysphoric disorder, are characterized by disorganization of internal rhythms. Disruption of the circadian timing system can manifest in several ways. The amplitude of an oscillation can be altered, notably through changes in: (i) the number of SCN neurons or their connections with other brain areas or peripheral targets; or (ii) the neuronal traffic to the effector systems. The phase of the rhythms can also be altered, or there might be a partial or complete failure to remain driven by the prevailing light-dark cycle through disruption of neuronal input pathways that impose 24-h rhythmicity on the intrinsically non–24-h, rhythmic SCN. A very large number of physiological variables showing circadian abnormalities in depressed patients are described in the literature. Alterations in circadian rhythms in body temperature, hormone secretions, and vigilance state very often accompany endogenous depression.³⁶,³⁷ and unavoidable alterations in normal circadian rhythms can trigger depressive episodes in human.³⁸ Most rhythms are phase advanced with respect to the sleep-wake cycle, diminished in amplitude, and/or show day-to-day variability in entrainment. Although altered rhythmicity could be either a cause or an effect of an altered affective state, the high...
prevalence of circadian dysfunction in affective states suggests that the circadian system holds important clues regarding the etiology and treatment of affective disorders.

Much less attention has been paid to variations in circadian amplitude than to those affecting phase and period, but there has been increasing recognition that blunted circadian amplitude may be one of the main chronobiological abnormalities in depression. This suggests that novel treatments addressing such abnormalities could have potential value in the management of depression, and that melatonin could be a target for antidepressant therapy.

**Melatonin: a target for antidepressant therapy**

Melatonin (N-acetyl-5-hydroxytryptamine) is an endogenous neurohormone secreted by the pineal gland, whose circadian and nocturnal secretion is controlled by the SCN through β-adrenergic receptors. Melatonin is an endogenous synchronizer of biological rhythms in mammals and its secretion and actions are tightly related to seasonal and light-dark cycles. Melatonin’s ability to control circadian rhythm synchronization has triggered numerous studies seeking to determine its role in the pathogenesis of various psychiatric disorders, including depression.

Given the extensive perturbations of circadian rhythms in depressive disorders on the one hand, and the chronobiologic properties of melatonin on the other, it was logical to expect that melatonin would exhibit potential clinical benefits. Such hopes were encouraged by reports of alterations of melatonin secretory patterns in various psychiatric disorders. Both decreases and increases in melatonin plasma levels have been evidenced in depressed patients. Both a familial vulnerability in the endogenous melatonin signal in subjects prone to depression and an abnormal duration of the melatonin signal in subjects with current major depression have been hypothesized.

Preclinical studies have demonstrated that melatonin is active in several experimental models responsive to antidepressant treatment (Table I). This antidepressant-like activity of melatonin has been demonstrated, in particular, during repeated nighttime administration in a “chronic mild stress” paradigm with diurnal and sleep rhythm disruptions, in both C3H/He mice and rats. In addition, melatonin, like effective antidepressants, is active in the forced swimming test and N-acetyltransferase “knocked-down” C57BL/6J mutant mice display a longer immobility time in this test, regardless of circadian rhythm.

Although most clinical studies have pointed out the presence of melatonin secretion disturbances in depressed patients, the link between melatonin and clinical depressive states remains unclear. Nevertheless, a relationship between melatonin levels and depression has been reported by Souetre et al who found a correlation between low concentrations of circulating melatonin and the Hamilton Depression Rating Scale (HDRS) scores in a population of patients with symptomatic major depression and another population in remission. Krahn et al also reported that successful ECT in patients with major depression is associated with a decrease in 6-sulfatoxymelatonin urinary excretion.

However, other authors have attempted to find correlations between the clinical manifestation of depression, intensity of symptoms, and the course of the disease on the one hand, and melatonin secretion disturbances on the other. More recently, Szymanska et al have shown that plasma melatonin levels do not differentiate patients in terms of severity of the depressive symptoms, abnormal levels being observed in patients with major depression as well as in patients in the remission phase. Nevertheless, changes in urinary excretion of 6-sulfatoxymelatonin have been reported to enable the distinction between antidepressant responders and nonresponders.

In contrast, other authors hypothesize that the efficacy of antidepressants of different classes (desipramine, fluvoxamine, mianserin, venlafaxine) is attributable to the enhancement of melatonin secretion (which could involve monoaminergic mechanisms acting on the pineal gland) and/or the inhibition of the degradation of melatonin.

**Table I. The antidepressant activity of melatonin, 5-HT2c antagonists, and agomelatine.**

<table>
<thead>
<tr>
<th>Model</th>
<th>Melatonin</th>
<th>5-HT2c antagonist</th>
<th>Agomelatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Despair test</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Learned helplessness</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Bullectomy</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Chronic mild stress</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Transgenic model</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Isolated aggressive mice</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Marble burying test</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Since melatonin has resynchronizing effects in both animals and humans suffering from circadian rhythm disorganization, the exciting possibility was raised that a drug able to mimic the effects of this neurotransmitter and easily cross the blood-brain barrier would be beneficial in the treatment of depression. This hypothesis led to the synthesis of agomelatine.

**Agomelatine: a new antidepressant with a novel mechanism of action**

Agomelatine (S 20098) is a potent ligand of melatonin receptors, with agonist properties at cloned human melatonergic MT1 and MT2 receptor level. In addition, it is also endowed with antagonist properties at cloned human 5-HT2c and 5-HT2c receptor level.
Melatonin agonist properties of agomelatine

Action on circadian rhythms

Behavioral studies in rodents have shown that systemic administration of agomelatine could dose-dependently alter the functioning of the circadian clock. The chronobiologic properties of agomelatine were first demonstrated by its ability to mimic the action of melatonin in the synchronization of circadian rhythm patterns of locomotor activity, running wheel activity, and body temperature in rodents.\(^65,66\)

Agomelatine dose-dependently drives rhythms by setting up a circadian pattern in free-running animals. This ability to synchronize rest-activity rhythms in free-running animals requires the integrity of the SCN, lending further support to its action on melatonin receptors. In addition, agomelatine can reset a preexisting circadian rhythm following a phase shift, since it has the ability to faster reentrain rats following an 8-h phase advance of the light-dark cycle in vivo. These effects are dose-dependent, up to a maximum usually obtained with oral administration of 8 to 10 mg/kg in rodents.\(^67\)

Similarly, in aged animals, long-term treatment with agomelatine reduces the time needed for reentrainment following a phase advance in the light-dark cycle.\(^68\) Finally, in aged animals with reduced responsiveness to zeitgebers, agomelatine can restore the sensitivity of the circadian clock to environmental synchronizers.\(^69\)

Efficacy of agomelatine in animal models of depression

Interest in agomelatine has recently increased due to its potential use as a novel antidepressant agent, as demonstrated in a number of animal studies using well-validated animal models of depression (Table I).\(^53\) These findings support the potential use of agomelatine as an antidepressant in humans, and indeed, agomelatine has been shown to be clinically effective in depressed patients.\(^70,71\)

The antidepressant efficacy of agomelatine was first investigated using the forced swimming test. Both acute and repeated treatment with agomelatine (2, 10, and 50 mg/kg) showed an antidepressant effect in rats and mice, as evidenced by a significantly reduced duration of immobility at all doses tested. Results following agomelatine administration were comparable to those with imipramine and fluoxetine, whereas treatment with melatonin showed no effect.\(^21\)

The antidepressant efficacy of agomelatine was further investigated in a large series of experiments. Results from the learned-helplessness model of depression also demonstrated agomelatine to be an effective antidepressant. In this study, agomelatine (10, 50 mg/kg per os) was shown to be equivalent to imipramine in its ability to reverse the learning deficit caused by exposure to aversive stimuli. Once-daily administration was superior to twice-daily administration of agomelatine, with the most significant antidepressant effects being noted with the 10 mg/kg dose.\(^21\) The effects of agomelatine were also studied in the model of olfactory bulbectomized rats. Ambulation scores were statistically similar among animals treated with agomelatine (10 or 50 mg/kg) or imipramine (10 mg/kg). Both treatments effectively reduced, to the same extent, the locomotor hyperactivity caused by bulbectomy.\(^74\)

To date, the model of chronic mild stress is considered to be the most reliable model for identifying the antidepressant-like properties of drugs, because it focuses on anhedonia, one of the key symptoms of depression. In addition, antidepressants have to be administered on a chronic basis in order to reverse the induced behavioral deficits, in line with the delay in the onset of therapeutic action of these drugs. In this paradigm, rats are subjected for several weeks to unpredictable minor stress sessions that cause behavioral alterations, which closely resemble those most frequently observed in depressed patients. In particular, rats develop anhedonia, as shown by their decreased voluntary intake of a sucrose solution. Chronic IP administration of agomelatine (10 and 50 mg/kg daily) was compared with treatments with melatonin (10 and 50 mg daily) or the classic antidepressants imipramine (10 mg/kg daily) and fluoxetine (10 mg/kg daily), in this model of depression. Agomelatine reversed anhedonia induced by chronic mild stress, to a similar extent to that achieved by the other antidepressant drugs (Figure 1). Thus, agomelatine was found to be a potent and rapidly acting antidepressant in this model. Once installed, the effect of agomelatine was quite robust, with no withdrawal-induced relapse at 1 week after cessation of agomelatine treatment.\(^55\)

Interestingly, whether agomelatine was administered in the morning, ie, at the beginning of the light period, or in the late evening, just prior to the start of the dark period, had no influence on its capacity to restore the rats’ preference for sucrose, suggesting that the antidepressant-like properties of this drug involve mechanisms independent of circadian rhythms. In contrast, under the same conditions, melatonin was found to partially restore the rats’ preference for sucrose only when the neurohormone was injected just prior to the onset of the dark phase (Figure 1). This difference clearly indicates that the neurobiological mechanisms underlying the antidepressant-like action of agomelatine are not shared by melatonin. Indeed, blockade of melatonin receptors by the MT1/MT2 receptor antagonist S 22153 failed to reverse the antidepressant-like effect of agomelatine injected in the morning.\(^55\)

Finally, alongside agomelatine’s specific properties linked to its novel antidepressant profile of action, agomelatine was shown to exert a stimulatory influence on cell proliferation within the subgranular layer of the dentate gyrus in rats. Chronic administration of agomelatine (40 mg/kg IP daily for 21 days) significantly increased the number of cells labeled by BrdU (a thymidine analog that is incorporated in DNA synthesized during mitosis) in adult rat brain, within a circumscribed region of the hippocampus, the ventral part of the subgranular layer.\(^77\) A 3-week treatment with agomelatine (10 or 50 mg/kg IP daily) also reversed the deficit in granule cell proliferation that had been induced in adult rats from a mother subjected to repeated stress during gestation.\(^78\) With regard to cell proliferation in the dentate gyrus, agomelatine therefore acts like all other antidepressant therapies tested to date.
to a more or less significant extent, to the antide-
pressant efficacy. Using a classic receptor agonist, extensive studies have identified an-
other mode of action for this drug. Using a classic test setting for 5-HT2C antagonists, agomelatine was found to antagonize the penile erections normally induced by 5-HT2C receptor activation in Wistar rats. Penile erections were induced by administration of the 5-HT2C receptor agonists mCPP and Ro-60-0175, and diminished, in a dose-dependent manner, when agomelatine was added. In contrast, melanotin administration had no effect in this paradigm. It was therefore concluded that this effect of agomelatine did not involve its melatonin receptor agonist prop-
erties, but, instead, that it was due to 5-HT2C recep-
tor antagonism.

Recent results from receptor binding and signal-
ing studies have lent further support to the hypoth-
esis of a secondary mode of action for agomela-
tine. Analyses of receptor binding in transfected Chinese hamster ovary (CHO) cells showed that agomela-
tine acts as an antagonist at both the 5-HT2C and 5-HT3B receptor subtype level. Agomelatine, there-
fore, has a unique pharmacological profile, result-
ing from stimulation of MT1 and MT2 receptors and blockade of 5-HT2C and 5-HT3B receptors. In vivo experiments in relevant animal models (see above) have clearly demonstrated the reality of 5-HT2C receptor blockade with agomelatine at doses used to elicit antidepressant-like effects. In contrast, very little is known to date regarding 5-HT3B receptor blockade and its possible behavioral consequences in vivo (on food intake, sleep, etc.). Thus, whether or not blockade of the 5-HT3B receptor subtype, which is expressed at low levels in the brain, contributes, to a more or less significant extent, to the antide-
pressant effects of agomelatine, is a question which cannot be answered at present.

All new antidepressants for which new mech-
nisms of action are claimed should be investigated for the presence of possible interactions with mono-
aminergic systems, since it is unlikely that antide-
pressant efficacy can be achieved without recruit-
ing monoaminergic mechanisms, either directly or indirectly by actions upstream or downstream of monoaminergic neurons. Because of its 5-HT2C recep-
tor antagonist properties, both acute and chron-
ic administration of agomelatine (10–40 mg/kg IP) produce concomitant dopamine and NE overflow in the frontal cortex.77 It can be assumed that the stimulatory effect of agomelatine on these mono-
aminergic systems also contributes to its antide-
pressant action, since these neurotransmitters mod-
ulate cognitive-attentional performance and mood in the frontal cortex. On the other hand, 5-HT out-
flow is unchanged by agomelatine treatment, which indicates that mechanisms underlying its antide-
pressant-like action are totally unrelated to those of tricyclics, SSRIs, and MAOIs,78,79 which all gen-
erally elicit a marked increase in 5-HT outflow.

**Conclusion**

New antidepressants based on other mechanisms of action than the monoamine hypothesis are a pro-
mising approach in the development of drugs with better tolerance and efficacy. One of the most ex-
citing prospects in the treatment of depression has been the development of the new antidepressant agomelatine, a compound that exhibits strong melato-
in receptor agonist activity and 5-HT2C receptor antagonist properties. This unique combination of pharmacological properties very probably explains the efficacy of agomelatine observed in all validat-
ed animal models of depression. Agomelatine thus represents a new concept in the treatment of de-
pression, and provides a strong incentive for the development of antidepressant drugs with mixed mechanisms of action encompassing monoaminergic as well as nonmonoaminergic systems.
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Perspectives nouvelles dans la physiopathologie et le traitement des troubles affectifs: le rôle de la mélatonine et de la sérotonine

Depuis plus de 40 ans, la recherche sur la pathogenèse de la dépression et le développement de médicaments adaptés pour un traitement efficace a été dominée par l’hypothèse monoaminergique, qui stipule que la dépression implique un déséquilibre en sérotonine, noradrénaline, et probablement en dopamine. Bien que ces neurotransmetteurs monoaminergiques – dont les rôles respectifs sont passés en revue – soient impliqués de façon indiscutable, le déficit en monoamines ne rend compte seulement que d’une partie des faits, et d’autres événements hormis le déséquilibre monoaminergique devraient être pris en compte. Il existe un besoin évident de médicaments antidépresseurs plus efficaces, mieux tolérés et d’action plus rapide. Le développement de nouveaux antidépresseurs dont le mécanisme d’action repose sur d’autres bases que l’hypothèse monoaminergique est très prometteur. Cet article souligne l’impact de la mélatonine et de ses récepteurs sur la dépression et présente un antidépresseur développé récemment possédant une efficacité clinique démontrée, l’agomélatine. Ce produit, qui se distingue par des propriétés agonistes de la mélatonine et antagonistes des récepteurs 5-HT2C, représente un nouveau concept dans le traitement de la dépression.
Severe depression: from diagnosis to treatment

by J.-P. Olié, France

Severe depression comes in a variety of presentations, from highly acute intense depression to chronic refractory states complicated by predisposition or comorbidity. Current antidepressants are often ineffective in depression with somatic or psychiatric comorbidity, psychotic symptoms, or imminent threat to life. Pharmacologic efficacy in severe depression is difficult to demonstrate in children and the elderly for methodological reasons. New antidepressants are as much needed as ever, among other reasons to advance our understanding of the etiopathogenesis of depressive disease and the mechanism of antidepressant action: an acute increase in synaptic cleft monoamine levels is a clearly inadequate guide either to understanding depression or to choosing appropriate drug therapy. Improved tolerability, shortened time to effect, and efficacy in relieving cognitive and somatic symptoms in emergency (life-threatening) situations are the criteria for evaluating any potential new antidepressant.


Keywords: severe depression; childhood depression; depression in the elderly; antidepressant; treatment

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In this type of situation, ECT may be necessary, in particular as malnutrition, dehydration, suicidal intent, and repeated attempted suicide all predict a favorable response.2 Endogenicity and melancholia, on the other hand, are poorer predictors, in contrast to long-held belief.2 The best predictor of response to ECT is psychomotor retardation.4 In any event, ECT is mandatory in imminently life-threatening depression, in particular because of its rapid onset of effect and the risks of imipramine therapy. This underlines the need to identify drugs that can act rapidly and safely in the (often malnourished) elderly.

The problem of time to antidepressant effect is clearly critical in severe depression, in particular when there is an imminent threat to life. At present, various chemotherapy strategies can be used to lower suicide risk: restoration of the sleep-wake cycle using a hypnotic may help to relieve the depression and pressure of suicidal ideas; reduction of anxiety using an anxiolytic can prevent impulsive suicide (in this context, benzodiazepines, with their potential for paradoxical disinhibitory reactions, are best avoided in favor of other types of anxiolytic, eg, levomepromazine or cyamemazine); suicidality may also respond to drugs such as lithium.

It is generally agreed that the efficacy of an antidepressant can only be assessed after treatment for 4 to 6 weeks. Certain effects may emerge earlier, of course, heralding greater efficacy at 6 weeks.5 Tolerability becomes crucial where the threat to life is physical. Posttricyclic antidepressants marked a significant advance in this regard. Safety—cardiac, hepatic, and neurologic—is mandatory. The new antidepressants are generally much easier to use than their predecessors, although renutrition and gentle sedation often remain necessary to bridge the gap until the onset of antidepressant effect. Under such conditions, the ideal antidepressant is one with rapid onset of effect against anxiety and suicidality, combined with a high level of tolerability.

**Depression with psychiatric comorbidity**

Clinical depression can be associated with psycho-behavioral symptoms that reverse on effective antidepressant treatment. They include obsessive symptoms, eating disorders, irritability, and pathological personality traits.

Depression may also feature in the natural history of anxiety disorder or personality disorder. The classic example is that of panic disorder complicated by a depressive episode: panic disorder can be diagnosed in 20% to 30% of patients with depression; as a severity factor, it carries considerable psychosocial impact, with a high risk of suicide.4 However, the prognosis may be better if depression precedes panic disorder.5 Depression is often associated with generalized anxiety disorder: early-onset anxiety disorder may be a severity factor for anxiety and depression.4

Depressed patients with personality disorder differ in several ways from those without: earlier-onset mood disturbance, less social support, more often single or divorced, more hospital admissions, and more severe depressive symptoms with higher suicidality. The personality disorder also compounds treatment resistance. An antidepressant that would not only remain effective despite such comorbidity, but could also treat it, would have a definite advantage.

**Depression with psychotic symptoms**

Mood-congruent and non—mood-congruent are not categories cast in stone—they can be influenced by sociocultural factors.9 For some psychiatrists, the concept of psychotic depression partly overlaps that of endogenous depression. Should depression be viewed as a continuum, stretching from nondelusional depression (Kraepelin’s simple melancholia) to severe delusional depression or delusional melancholia? Or should delusional depression be considered a specific category?10

Comparison between delusional and nondelusional depression reveals no differences in sex, age of onset, number of episodes, or number of suicide attempts. However, cluster A personality disturbances appear more frequent in delusional depression, and cluster B disturbances more frequent in its nondelusional counterpart.11 Some psychiatrists find delusional depression more frequent in bipolar than in unipolar patients.12 Delusions may increase the risk of suicide, in both bipolar and unipolar depressives.13 The risk of mood disturbance in first-degree relatives may be higher in delusional than in nondelusional depression.14

Delusions and hallucinations reach critical levels in the most serious forms of depression in which obnubilation facilitates the emergence of terrifying interpretative visions and delusional ideas. Such delusional presentations have become rare, probably aborted by psychotropic agents. Thus full-blown Cotard syndrome, in which delusional negation of organs or the entire body is combined with delusional ideas of eternal damnation and immortality, and the negation of family, space, and time, now tends to be replaced by partial presentations, eg, delusions of damnation or individual organ negation. No antidepressant has proved as effective in delusional depression as in its nondelusional counterpart.

Psychotic symptoms are significantly more frequent in adolescents15 and preadolescents,16 posing a differential diagnostic quandary with incipient schizophrenia and raising awkward management problems: older antidepressant alone, newer antidepressant alone, or either in combination with an antipsychotic?

The concept of schizoaffective disorder introduced by Kasanin in 1933 raised classification problems that remain unresolved. In terms of prognosis, depressive schizoaffective disorder falls midway between schizophrenia and major (psychotic) depression.17 Here too, treatment is often mixed, combining an antidepressant with an antipsychotic.
**Depression in children and adolescents**

Although midterm outcome is often favorable, the prognosis of depression in the young is often poor, with 75% relapse at 5 years, thus considerably increasing the risk of depression in adulthood. In addition, comorbidity is high, with character or behavioral traits that can interfere with the diagnosis of depression and also its treatment. Hostility by the child or adolescent generates a vicious circle of hostile communication that feeds, perpetuates, and even amplifies the underlying disorder. This may trigger risk-taking behavior. In addition, environmental factors can play a major role in facilitating suicidal behavior. A history of depressive episode in childhood is a risk factor for attempted suicide in adulthood. There is also the diagnostic quandary mentioned earlier: how to differentiate between mood disorder on the one hand and depression in an incipient chronic schizophrenic on the other? It is still difficult to demonstrate antidepressant efficacy in child and adolescent depression.

**Depression in the elderly**

In the elderly, it is mandatory to test for degenerative disease when depression coexists with psychosis, especially if there is no history of depression. Delusional hypochondriasis becomes more frequent with age. Severe cases may present with confusion, or more commonly hallucinations that can be psychic, auditory-verbal, visual, or involve bodily sensations.

Cognitive and depressive symptoms are frequently intertwined in this age group. Over 25% of dementia patients first present with altered mood. The term depressive pseudodementia is widely used to reflect the depression/dementia interface. There are five main clinical variants: (i) depression with low-grade cognitive impairment; (ii) depressive dementia; (iii) nondepressive dementia; (iv) dementia-induced depression; and (v) comorbidity.

In addition to increased suicide risk in the elderly, the two other factors that compound depression in this age group are cognitive impairment, which increases risks such as dehydration, and organic brain disease, which causes antidepressant resistance and heralds dementia. Because concomitant physical ailments are so common, it is essential to select an optimally tolerated antidepressant. The dream drug in such cases is one that would remain effective despite organic and psychiatric comorbidity, relieve cognitive impairment, and arrest the risk of dementia, and even—for good measure—correct the biological parameters that tend to decline with age.

**Treatment strategies**

No one antidepressant has proved more effective than the others, including severe depression. Certain markers of endogeneity may predict a good response to antidepressants: absence of mood reactivity to the environment, circadian variation, psychomotor retardation, anorexia, and weight loss. Resistance may simply reflect greater severity. Various treatment strategies are available:

- Increasing the dose of antidepressant (the advantages of this approach were shown with venlafaxine).
- Using a different antidepressant, including a monoamine oxidase inhibitor (MAOI).
- Combining two drugs with complementary pharmacologic effects, eg, an SSRI with an β-blocker (mianserin, mirtazapine).
- Combining an antidepressant with lithium.
- Combining an antidepressant with T3 thyroid hormone.
- Combining an antidepressant with a partial serotonin 1A receptor agonist.
- ECT is the last resort, the only therapy that has proved superior to an antidepressant. In severe depression the predictors of response to ECT are: Presence of melancholic symptoms.
- Threat to life (malnutrition, high suicide risk).
- Psychotic symptoms.
- Catatonic symptoms.
- Pregnancy or severe postpartum depression.
- Advanced age.

This highlights the urgent need for new antidepressant treatments that ideally:

- Advance our understanding of the mechanism of mood-elevating activity: this requires the development of drugs with novel neurobiologic actions, given that the mere increase in monoamine levels in the synaptic cleft is a far from adequate account of antidepressant effect.
- Can be tailored to a patient or a type of depression; a current difficulty is our inability to predict which antidepressant will actually be best for a particular patient or for a particular phase in the disease.
- Restore normal psychological and social function by doing more than achieving symptom remission.

If such drugs could be identified, today’s severe depression could be more easily treated and no doubt prevented.

**REFERENCES**

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DéPRESsIOn SÉvÈRe : DU DIAGNOSTIC AU TRAITEMENT

La notion de dépression sévère est polysémique, recouvrant aussi bien des dépressions particulièrement aiguës et intenses que des états difficiles à traiter en raison d’un terrain particulier ou d’une comorbidité. Les dépressions avec comorbidity somatique ou psychiatrique, avec symptômes psychotiques, avec risque vital imminent sont souvent peu efficacement traitées avec les antidépresseurs aujourd’hui disponibles. Chez l’enfant et le sujet âgé des difficultés méthodologiques rendent difficiles la démonstration d’efficacité d’un agent pharmacologique dans la dépression sévère. Ainsi de nouveaux antidépresseurs restent-ils nécessaires. Ils devraient aider à progresser dans la connaissance étiopathogénique du trouble dépressif et du mécanisme d’action des antidépresseurs, l’augmentation aiguë de taux de monoamines dans la fente synaptique ne pouvant, à l’évidence, suffire à guider notre compréhension du trouble dépressif et le choix de nos prescriptions. L’amélioration de la tolérance, mais aussi le raccourcissement du délai d’action et l’efficacité dans des contextes d’urgence (risque vital) sur des symptômes tels que les symptômes cognitifs et somatiques sont des objectifs à la lumière desquels doit être évaluée toute nouvelle molécule potentiellement antidépressive.
Shortcomings of current antidepressant therapies

by S. H. Kennedy, Canada

The chapter reviews patient variables that influence treatment outcomes in Major Depressive Episode (MDE), before focusing on the current limitations of today's antidepressant options.

**Treatment of depression: patient variables**

- **Compliance**
  Compliance reflects the positive or negative interactions among patient, drug, and prescriber variables and is a significant, but frequently neglected, reason for poor treatment outcome. Results from primary care studies indicate that fewer than 50% of depressed patients continue to take their medication after 12 weeks.1,2 The reasons cited in both studies are remarkably similar in content and frequency (Table I).

Successful treatment of a Major Depressive Episode (MDE) is influenced by many factors beyond the properties of a particular medication. These include the unique characteristics of each patient; the safety–tolerability–effectiveness profile of the drug, and the interaction between patient and health care professionals. While newer antidepressants represent considerable advances in safety and tolerability compared with tricyclic (TCA) and monoamine oxidase inhibitor (MAOI) agents, the improvement in therapeutic benefit is not substantial. The delay to achieve antidepressant benefit, the percentage of patients who do not reach response or remission criteria, the persistence of unwanted side effects, and concerns about drug discontinuation emergent effects are all shortcomings of current antidepressants.

**Keywords:** antidepressant; major depressive disorder; personality; compliance; onset of action; side effect

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>DESS</td>
<td>discontinuation emergent signs and symptoms</td>
</tr>
<tr>
<td>EPQ</td>
<td>Eysenck Personality Questionnaire</td>
</tr>
<tr>
<td>HRSD</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MDE</td>
<td>Major Depressive Episode</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NEO-PI</td>
<td>Neuroticism, Extraversion, and Openness Personality Inventory</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>TCI</td>
<td>Temperament and Character Inventory</td>
</tr>
</tbody>
</table>

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Address for correspondence: Sidney H. Kennedy, MD, FRCP, University Health Network, 200 Elizabeth St, EN8-222, Toronto, ON M5G 2C4, Canada (e-mail: sidney.kennedy@uhn.on.ca)
ty Questionnaire (EPQ), Temperament and Character Inventory (TCI), or the Neuroticism, Extraversion, and Openness Personality Inventory (NEO-PI). Although few in number, several studies have evaluated the influence of personality on help-seeking behavior, symptom presentation, compliance, and ultimately treatment outcomes. In most cases, neuroticism and extraversion account for differences in depressed patients.

For example, men in an urban setting who have a low level of neuroticism and an external attributional style are less likely to seek help than men with higher levels of neuroticism. With regard to symptom presentation, a high level of “harm avoidance” (equivalent to neuroticism) in both men and women has been shown to predict higher levels of severity, more physical symptoms including fatigue in depressed patients, while high “novelty seeking” (equivalent to extraversion) is associated with suicide attempts, impaired concentration, and alcohol abuse.

The influence of neuroticism on side-effect reporting was examined in a group of nonpsychiatric healthy volunteers who received moclobemide or placebo for 3 weeks under double-blind randomized controlled conditions. The strongest predictor of side-effect reporting was baseline neuroticism, and this relationship increased over time in the placebo group, but declined in the moclobemide group, again highlighting the importance of variables beyond pharmacokinetic and pharmacodynamic properties of the drug.

The relationship between neuroticism and treatment response has also received considerable attention. In a large primary care trial involving more than 300 patients who met diagnostic criteria for dysthymia, Katon and colleagues reported that a high baseline level of neuroticism was associated with better compliance during fluoxetine treatment. Using the Diagnostic and Statistical Manual of Mental Disorder, 3rd Edition, Revised (DSM III-R) designation of cluster A (Paranoid, Schizoid, and Schizotypal), cluster B (Antisocial, Borderline, Histrionic, and Narcissistic), and cluster C (Avoidant, Dependent, and Obsessive-Compulsive) personality disorder, Fava and colleagues examined the predictive value of personality disorder comorbidity in patients who received fluoxetine. There were no differences in rates of response between patients with or without a cluster A or C diagnosis, while the presence of a cluster B diagnosis before treatment predicted a positive antidepressant response. Almost a decade later, Mulder and associates examined the interaction between antidepressant class selection (fluoxetine or nortriptyline), personality disorder (presence or absence) and drug response. Although the presence of a comorbid personality disorder did not have an overall effect on outcome, those patients with a cluster B personality had a significantly better response to fluoxetine compared with nortriptyline.

While others have reported less favorable outcomes for depressed patients with personality disorders during continuation therapy, the weight of evidence suggests that such comorbidity does not adversely affect outcome.

### Comorbid personality disorders

A related question is whether or not patients with a diagnosis of MDE and a comorbid personality disorder have a worse outcome during antidepressant treatment. Using the Diagnostic and Statistical Manual of Mental Disorder, 3rd Edition, Revised (DSM III-R) designation of cluster A (Paranoid, Schizoid, and Schizotypal), cluster B (Antisocial, Borderline, Histrionic, and Narcissistic), and cluster C (Avoidant, Dependent, and Obsessive-Compulsive) personality disorder, Fava and colleagues examined the predictive value of personality disorder comorbidity in patients who received fluoxetine. There were no differences in rates of response between patients with or without a cluster A or C diagnosis, while the presence of a cluster B diagnosis before treatment predicted a positive antidepressant response.

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While others have reported less favorable outcomes for depressed patients with personality disorders during continuation therapy, the weight of evidence suggests that such comorbidity does not adversely affect outcome.

### Table I. Reasons cited for discontinuation during 12 weeks of antidepressant treatment.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling better</td>
<td>55%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>33%</td>
</tr>
<tr>
<td>Fear of dependence</td>
<td>10%</td>
</tr>
<tr>
<td>Stigma</td>
<td>10%</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling better</td>
<td>35%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>30%</td>
</tr>
<tr>
<td>Other reasons</td>
<td>17%</td>
</tr>
<tr>
<td>Physician instruction</td>
<td>15%</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>15%</td>
</tr>
</tbody>
</table>

Mr T worked in the sales department of a brewing company. He was a particularly gregarious individual. Over a 6-year period, he had been seen by three different primary care physicians. On each occasion, he presented with typical symptoms of a major depressive episode. For him, the most prominent symptom was losing interest in his normally active social life.

There was also a pattern to his antidepressant usage. Typically, he responded very quickly, often during the first week. He would regain interest in social activities and increase his success in sales. At about the same time, he would start to miss doses of his antidepressant medication for days at a time and eventually stop altogether.

Only after a detailed discussion about the potential negative relationship between his outgoing personality style and medication compliance did Mr T agree to comply with antidepressant therapy and he has remained well for the past 2 years.
Shortcomings of current antidepressant therapies – Kennedy

Unmet Needs in the Treatment of Depression

◆ Severity of illness

Since there is really no consensus on what constitutes “severe depression,” it is difficult to reach a conclusion about its impact on treatment outcome. A predetermined baseline score on the Hamilton Rating Scale for Depression (HRSD)\(^1\) such as scoring 24 or higher at baseline on the 17-item HRSD, or a score above 28 at baseline on the Montgomery-Asberg Depression Rating Scale (MADRS),\(^2\) are frequently applied criteria for “severe depression.” It must be pointed out, however, that different symptom weighting on these scales (eg, there are 3 sleep items on HRSD and 1 sleep item on MADRS) may result in some patients being considered “severe” on one scale, but not on another.

Figure 1. Physician-reported preferences for antidepressants: the most significant disadvantage of the most frequently prescribed antidepressant.

Relatively few studies have been designed to examine the relationship between severity of symptoms and preferential drug response, although it is generally believed that antidepressant treatments are less likely to prove superior to placebo in patients with low pretreatment scores.\(^1\)\(^2\) Clinical impression that moclobemide is less effective in severe depression was initially supported in a global review of moclobemide trials, in which imipramine was superior to moclobemide in the group with baseline HRSD scores of 28 or higher,\(^2\) but not confirmed in a subsequent analysis using the same drug.\(^2\) Greater efficacy in more severely depressed patients is a desirable characteristic of any antidepressant. Khan and colleagues\(^1\) have also examined the relationship between severity of depressive symptoms and response to a range of selective serotonin reuptake inhibitor (SSRI) antidepressants, venlafaxine, nefazodone, and placebo. Pretreatment severity was assessed using the 17-item HRSD, and patients were categorized into 4 groups according to baseline scores. The drug-placebo difference from baseline to end of treatment (effect size) was progressively greater as baseline severity increased.

◆ Melancholic and psychotic features

Other considerations that likely overlap, but are not synonymous with severity, include inpatient status and the presence of psychotic or melancholic features. While most would agree that a diagnosis of MDE with psychotic features warrants different treatment interventions, including combination antidepressant-antipsychotic medications or an early intervention with electroconvulsive therapy,\(^2\) there is less consensus on the relevance of melancholia. In a natural practice setting, where patients completed standard diagnostic and severity measures, melancholic patients had lower response rates to paroxetine, sertraline, and venlafaxine compared with nonmelancholic patients (48% vs 61%).\(^2\) In this study, there was no difference in rate of response among drugs in the melancholic subgroup. However, there is evidence that TCAs, in particular clomipramine, were more effective than SSRIs in treating melancholic depression (see Amsterdam for a review). In subsequent trials, venlafaxine was superior to placebo\(^2\) and fluoxetine\(^2\) in hospitalized patients with melancholia. Interestingly, Guelfi and colleagues\(^1\) also reported similar outcomes when mirtazapine was compared with venlafaxine in hospitalized severely depressed patients with melancholic features.

There are also differences between outpatient and inpatient groups in their response to TCA and MAOI antidepressants. In a meta-analysis, Thase and colleagues\(^2\) reported superior response rates to MAOI antidepressants compared with TCAs among outpatients, while the converse was true for inpatients. Likewise, a group of Danish investigators, using clomipramine as the active comparator, consistently reported its superiority over the reversible inhibitor of MAO-A, moclobemide,\(^2\) as well as two SSRIs—paroxetine\(^2\) and citalopram\(^1\)—in studies involving depressed inpatients. However, a variety of factors including suicidality, social supports, and differences in practice patterns across countries, influences the decision to admit a depressed patient to hospital.

In summary, shortcomings of current antidepressant therapies need to be considered in the context of treatment adherence, distinct patient profiles including personality differences, and illness severity. One or more of these variables often contribute to poor treatment outcome.

Unmet needs with current therapeutic choices

The widespread use of SSRIs to treat patients with depression in primary care and specialist settings represents a significant advance in managing one of the most functionally disabling and frequently comorbid medical conditions.\(^5\) With greater safety and tolerability compared with TCA and MAOI agents, compliance with SSRI and newer antidepressants during acute and maintenance phases has improved, and the percentage of depressed patients who are hospitalized for treatment continues to decline.\(^2\) Even so, there are still considerable limitations to SSRI and dual action (duloxetine, venlafaxine, bupropion, milnacipran, and mirtazapine) antidepressant agents.

The “therapeutic lag” between initiating treatment and achieving clinically meaningful effects...
Physicians across Europe identified slow onset of action as the most problematic issue in current antidepressant therapy, but also highlighted side effects and predictability of response as significant shortcomings of current agents (Figure 1). There is no overall increase in the percentage of responders to SSRIs compared with TCAs, with a full third of patients in most clinical trials showing an unsatisfactory response and less than 50% achieving full symptomatic remission.

**Therapeutic delay**

Antidepressants with a faster onset of action would offer significant benefits to patients. A rapid improvement in sleep would reduce the need for co-prescription of hypnotic medications and may decrease suicidal ideation in the critical early weeks of treatment. Although serotonin reuptake occurs almost immediately after antidepressant administration, onset of antidepressant action is often 2 to 3 weeks later. This coincides with the 2- to 4-week latency for adaptational downregulation of presynaptic 5-HT1A receptors, which results in a net increase in 5-HT release to frontal cortex and limbic areas. This latency has also been linked to hippocampal neurogenesis and other molecular changes in gene expression associated with antidepressant treatment.

Based on understanding of 5-HT1A neurophysiology, pindolol, a 5-HT1A antagonist and β-blocker, has been administered with various SSRIs to accelerate and augment the effect of SSRIs via blockade of 5-HT1A autoreceptors. Although results have been inconsistent, this may be partly explained by differences in patient characteristics. An accelerated response was seen in previously untreated patients, with a relatively short duration and low severity of depression and few prior episodes (see review by Segrave and Nathan). A further explanation of the inconsistent results obtained with pindolol relates to adequacy of the usually prescribed dose to bind at 5-HT1A sites. The extent to which mirtazapine and escitalopram may produce an accelerated response is a matter for further exploration.

**Side effects**

Side effects with SSRIs and dual action agents, although different from those with TCAs, are nevertheless substantial and frequently lead to premature drug discontinuation. Anticholinergic and cardiovascular side effects are most prevalent with TCAs, while gastrointestinal and central nervous system side effects are more problematic with SSRIs. Dual action agents differ in side effect profiles according to their mechanism of action.

Weight gain and sexual dysfunction are probably the most unacceptable long-term side effects for many patients. Since there are no randomized multiple drug, placebo-controlled trials from which to derive comparative rates of side effects, it is necessary to rely on drug-placebo differences in side effect reports as a crude method to compare different antidepressants.

- **Selective serotonin reuptake inhibitor antidepressants**
  - Greater tolerability and easy once-daily dosing have contributed to the widespread adoption of SSRIs as first-line therapy. There are six SSRIs available to treat depression in most countries: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. All of these agents block the reuptake of serotonin, but with differing degrees of selectivity and potency. Gastrointestinal side effects, especially nausea, are common during the first 1 to 2 weeks of treatment, but usually remit while other central nervous system effects including alterations to sleep architecture may persist. Relative frequencies of side effects are reported in Table II.

- **Dual action antidepressants**
  - Venlafaxine, milnacipran, and duloxetine inhibit both 5-HT and norepinephrine (NE) reuptake, while mirtazapine acts on both systems through indirect noradrenergic mechanisms. The side effects associated with SSRIs and dual action antidepressants are more problematic, but also differ in profile. Anticholinergic and cardiovascular side effects are more prevalent with TCAs, while gastrointestinal and central nervous system side effects are more problematic with SSRIs. Dual action agents differ in side effect profiles according to their mechanism of action.

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**Table II.** Frequently reported side effects across selective serotonin reuptake inhibitors (SSRIs).

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Incidence of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>None</td>
</tr>
<tr>
<td>Escitalopram*</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Sexual disturbances</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>GI distress</td>
</tr>
<tr>
<td></td>
<td>Sexual disturbances</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Paroxetine</td>
<td>Sexual disturbances</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>GI distress</td>
</tr>
<tr>
<td></td>
<td>Sexual disturbances</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

*Escitalopram is the stereoisomer of citalopram—comparable side effects to citalopram have been reported.
†GI, gastrointestinal.

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Shortcomings of current antidepressant therapies – Kennedy

When structured questionnaires are used to evaluate sexual dysfunction, 30% to 50% of patients who are treated with SSRIs or venlafaxine (comparable duloxetine data are not yet available) report impairment of desire and orgasm on SSRIs, while bupropion, mirtazapine, and moclobemide cause significantly less dysfunction (Table IV). A potential advantage of the tendency for SSRIs to delay ejaculation has been demonstrated in the treatment of premature ejaculation. The development of future antidepressants with favorable effects on sexual function would be valued by depressed patients and their partners.

**Weight gain across antidepressant classes**

Until recently, weight change received minimal attention as an outcome measure in antidepressant studies, although the tendency for TCA and MAOI agents to cause substantial weight gain has been recognized for many years. It is estimated that treatment with some TCAs resulted in a weight gain of approximately 1 kg per month (reviewed in Kennedy et al). While the SSRIs are frequently associated with modest reductions in weight during the acute phase of treatment, there is some evidence that weight gain may occur during maintenance treatment with some, but not all, SSRIs. Moclobemide and bupropion SR do not appear to be associated with weight gain during maintenance treatment and for some patients may be associated with weight reduction. Short-term trials suggest that venlafaxine is weight-neutral; however, there is an absence of controlled data on long-term weight change.

Among the currently available SSRI and dual action agents, mirtazapine is most likely to be associated with weight gain during acute treatment. This reflects both histaminergic and 5-HT2C receptor antagonist properties. During maintenance treatment with mirtazapine, patients who have not experienced weight gain in the acute phase are unlikely to start gaining weight, and those patients

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### Table III. Frequently reported side effects across dual action agents.


<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Incidence of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>GI distress</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Drowsiness, sedation</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Drowsiness, sedation</td>
</tr>
<tr>
<td></td>
<td>Disorientation/confusion</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Asthenia, fatigue</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Drowsiness, sedation</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>GI distress</td>
</tr>
<tr>
<td></td>
<td>Sexual disturbances</td>
</tr>
<tr>
<td></td>
<td>Drowsiness, sedation</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Asthenia, fatigue</td>
</tr>
<tr>
<td><em>GI, gastrointestinal.</em></td>
<td></td>
</tr>
</tbody>
</table>

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### Table IV. Frequency of sexual dysfunction during antidepressant treatment.


<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Incidence of sexual dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Citipram</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
</tbody>
</table>

who initially gained weight are likely to maintain a plateau after the first few months of treatment. Nevertheless, for many depressed patients, the prospect of substantial weight gain during antidepressant treatment represents an unacceptable health burden.

**Antidepressant discontinuation emergent effects**
Since the mechanisms of action of reuptake inhibitor antidepressants (SSRIs, SNRIs [serotonin and norepinephrine reuptake inhibitors], and others) involve adaptive downregulation early in the treatment process, it is not surprising that drug discontinuation, particularly abrupt discontinuation, would result in unpleasant rebound effects. In general, the shorter the half-life of the drug, the greater the likelihood of discontinuation emergent symptoms. Such occurrences are not limited to SSIRIs or dual action antidepressants. Cholinergic rebound was often observed following rapid discontinuation of amitriptyline or other TCAs with significant anticholinergic effects. Patients reported urinary frequency, headaches, hypersalivation, and diarrhea. Benzodiazepine withdrawal phenomena have also been recognized for many decades and include symptoms of insomnia, nausea, appetite loss, sweating, and dysphoria. Emerging symptoms associated with drug discontinuation of SSRIs or dual action agents have been observed most often when paroxetine or venlafaxine are stopped abruptly.57,58

In a double-blind, treatment interruption trial, patients who abruptly discontinued paroxetine and sertraline experienced significantly more discontinuation emergent signs and symptoms (DESS) compared with those who discontinued fluoxetine.57 The authors attributed differences in pharmacokinetic profiles among SSIRIs for the different rates of DESS. Similarly, high rates of DESS have been reported with venlafaxine compared with escitalopram 1 week after discontinuation.58 The effects of abrupt interruption of agomelatine, a new antidepressant with a unique melatonin agonist profile, were compared with interruption of paroxetine. Despite its short half-life of 2 hours or less,20 patients who discontinued agomelatine experienced significantly fewer DESS compared with those who discontinued paroxetine.60

**Conclusion**
Advances in neurogenetic and neuroimaging techniques have contributed to understanding the complex etiopathology of depression. Future challenges in drug development involve better matches between patient profiles and therapeutic targets, with an increased attention to drug tolerability and long-term safety.1

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Shortcomings of current antidepressant therapies — Kennedy

**LIMITES DES TRAITEMENTS ANTIDÉPRESSEURS ACTUELS**

L’efficacité du traitement d’un Épisode Dépressif Majeur (Major Depressive Episode, MDE) est soumise à de nombreuses influences au-delà des propriétés intrinsèques de tel ou tel médicament. Ces influences compensent les caractéristiques individuelles propres à chaque patient, le profil sécurité d’emploi/tolérance/efficacité du médicament. Ainsi qu’a l’interaction entre les patients et les soignants. Alors que les antidépresseurs récents ont permis des avancées considérables en termes de sécurité d’emploi et de tolérance mais en raison des effets secondaires de médicaments ou inhibiteurs de la monoamine oxidase (MAO), l’amélioration du bénéfice thérapeutique n’est pas probante. Le délai pour l’obtention du bénéfice antidépresseur, le pourcentage de patients non-répondeurs ou de ceux qui ne présentent pas de rémission, la persistance d’effets indésirables, et l’apparition d’effets émergents lors de l’arrêt du traitement soulignent les limites des antidépresseurs actuels.
Seasonal affective disorder: from diagnosis to treatment
by D. Winkler and S. Kasper, Austria

Physiological functioning of life on earth has over eons been influenced by the rising and setting of the sun. Likewise, it has been known since ancient times that seasonal changes in the environment affect humans’ physical and mental health: Hippocrates of Kos (460-377 BC) and Are- taeus the Cappadocian (about 150 AD) proposed the healing powers of sunlight for a range of somatic illnesses, but also for the state of melancholia.1 The majority of humans seem to experience seasonal variations of psychopathological symptoms to some extent.2 These seasonal changes are of clinical interest if their intensity leads to subjective suffering and a reduction in psychosocial functioning. Emil Kraepelin (1856-1926) was one of the first modern psychiatrists to become aware of a rise in the incidence of affective episodes in manic-depressive patients in spring and in fall. However, this finding was not much taken notice of until bright light therapy (BLT) was proposed as a possible treatment for winter depression by Lewy et al,3 followed by the first systematic study on seasonal affective disorder (SAD) by Rosenthal et al.4 Scientific research has been encouraged ever since and has led to the publication of more than one thousand studies on SAD and BLT, not only because SAD is clinically important, but also because it represents an important chronobiological paradigm.

Epidemiology

Numerous epidemiological studies have investigated the prevalence of SAD and of its subsyndromal form (s-SAD) in the general population (Figure 1, page 248).2,5-21 In temperate climates, about 2% to 5% of subjects seem to suffer from SAD, and the rate of individuals with minor problems during the fall-winter period indicating s-SAD is even higher. A number of reports have documented an increase in SAD prevalence with northerly latitudes.5-21 These findings are consistent with the hypothesis that seasonal changes in the environment affect humans’ physical and mental health.1,2,4

Seasonal affective disorder (SAD, fall-winter depression) is a subtype of major depressive or bipolar disorder, and has been a subject of psychiatric research for over two decades. The prevalence in the general population ranges between 2% and 5% in temperate climates, females are much more often afflicted by the syndrome. Atypical depressive symptoms with a reversed vegetative symptomatology predominate during the depressive episodes in the darker time of the year, while about one quarter of patients experience hypomanic (seldom manic) episodes during the successive spring/summer period. Bright light therapy (BLT) is generally accepted for depression in SAD, but psychopharmacological treatment with antidepressants has likewise been found to be effective and well tolerated. This article reviews the most important pathophysiological concepts and gives an overview of current diagnostic procedures and treatment options for SAD.

Keywords: seasonal affective disorder (SAD); winter depression; light therapy; antidepressant

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Clinical picture in seasonal affective disorder

The prevalence of SAD is higher in female than in male patients.24 In most clinical samples, women outnumber men by about 3.5:1 to 9:1,25 which is by far higher than the 2:1 ratio commonly found in nonseasonal depression.26 Psychiatric classification distinguishes between a winter type of SAD (fall-winter depression), and summer SAD,27,28 which is rare and will not be further discussed in this report. According to most clinical and epidemiological studies, the majority of patients experience their first affective episode in their late twenties or early thirties. The symptom pattern found in a clinical sample of 610 SAD patients is shown in Figure 2.
attacks, consisting of intense spells of inappropriate anger or rage. Furthermore, nearly half of all female SAD patients suffer from premenstrual dysphoric disorder (PMDD). The severity of seasonal depressive episodes ranges mostly between mild and moderate. However, severe depression, occasionally with suicidal ideations requiring inpatient treatment, is possible. About one quarter of SAD patients suffer from bipolar affective disorder with hypomanic or (rather seldom) manic episodes during spring or summer in addition to depressive symptoms during the fall-winter period.

Diagnostic procedure

As SAD is either a form of recurrent major depressive or bipolar disorder with onset and remission of the affective episodes at a specific time of the year, patients have to fulfill the diagnostic criteria of these disorders (see Table I for the diagnostic criteria for major depression). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised (DSM-IV-TR), it is possible to apply a seasonal pattern specifier to diagnose SAD (Table II).

The Global Seasonality Score (GSS), which is calculated from the Seasonal Pattern Assessment Questionnaire (SPAQ), has frequently been used to assess the degree of seasonal change in psychopathology in the past. According to the Rosenthal criteria, patients have to obtain a GSS of at least 10 to qualify for SAD. Furthermore, the overall degree of impairment during the worst time of the year has to be at least “moderate” to establish the diagnosis. This is the most important difference between SAD and s-SAD. Patients with the subsyndromal form report differences in several psychopathological items, however they experience no or only mild difficulties during fall and winter. The diagnostic criteria for s-SAD are presented in Table III. To examine the severity of seasonal depression, a modified version of the Hamilton Depression Rating Scale (HDRS) has been recommended: the Structured Interview Guide for the HDRS–SAD version (SIGH-SAD), which contains 29 items and covers not only melancholic symptomatology of depression, but also contains 8 items for atypical depression.

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### Table I. Diagnostic criteria for a major depressive episode according to DSM-IV-TR.


- **A.** Regular temporal relationship between the onset of major depressive episodes and a particular time of the year (unrelated to obvious season-related psychosocial stressors).
- **B.** Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year.
- **C.** Two major depressive episodes meeting criteria A and B in last 2 years and no nonseasonal episodes in the same period.
- **D.** Seasonal major depressive episodes substantially outnumber the nonseasonal episodes over the individual’s lifetime.

### Table II. Diagnostic criteria of the seasonal pattern specifier according to DSM-IV-TR.


- A. At least five of the following symptoms have been present during the same two-week period, nearly every day, and represent a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
  - **Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations
  1. Depressed mood (or alternatively can be irritable mood in children and adolescents)
  2. Markedly diminished interest or pleasure in all, or almost all, activities
  3. Significant weight loss when not dieting or weight gain or decrease in appetite
  4. Insomnia or hypersomnia
  5. Psychomotor agitation or retardation
  6. Fatigue or loss of energy
  7. Feelings of worthlessness or excessive or inappropriate guilt
  8. Diminished ability to think or concentrate, or indecisiveness
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- **B.** The symptoms are not better accounted for by a mood disorder due to a general medical condition, a substance-induced mood disorder, or bereavement (normal reaction to the death of a loved one).
- **C.** The symptoms are not better accounted for by a psychotic disorder like schizoaffective disorder

### Table III. Diagnostic criteria for subsyndromal seasonal affective disorder (s-SAD) according to Kasper et al.


- **A.** A history of some difficulty during the winter months that had occurred on a regular basis (at least two consecutive winters) and had lasted for a sustained period of time (at least 4 weeks).
- **B.** Examples of these difficulties are decreased energy, decreased efficiency at work (eg, concentration, completing tasks), decreased creativity or interest in socializing, and change in eating habits (eg, eating more carbohydrates), weight (gaining weight), or sleep patterns (more sleep).
- **C.** Subjects have to regard themselves as normal, ie, not suffering from an illness or disorder
- **D.** They have not sought medical or psychological help specifically for the above difficulties, nor has anyone else suggested that they do so
- **E.** People who do not know them well do not recognize that they have a problem, or if they do, easily attribute it to circumstances such as “flu” or “overwork”
- **F.** The symptoms experienced by the subjects have not disrupted their functioning to a major degree, eg, calling in sick several times per winter, or severe marital discord
- **G.** No history of major affective disorder in wintertime
- **H.** No serious medical illness

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Seasonal affective disorder: from diagnosis to treatment – Winkler and Kasper
sive symptoms, which are frequently found in SAD. For many patients it takes years until the correct diagnosis is made: the mean diagnostic latency in a German-speaking sample was approximately 10 years after the first depressive episode. This is still unacceptably long. However, since the early 1990s, the diagnostic latency has decreased by about 3 years, probably due to education of medical professionals and increased awareness of patients.

**Pathogenesis of SAD**

It is supposed that the shorter photoperiod during fall and winter triggers the onset of depressive symptoms in predisposed individuals. Light is one of the most important zeitgebers and is able to reliably alter the length and phase of the human circadian rhythm by affecting the main circadian pacemaker in the diencephalon, the suprachiasmatic nucleus. Scientific research has focused especially on the hormone melatonin (5-methoxy-N-acetyltryptamine), which is produced in the pineal gland and thought to mediate the photoperiod signal by the onset and duration of nocturnal secretion. Studies measuring dim light melatonin onset have found a phase delay in SAD patients that was successfully reversed with BLT. However, there is a subset of SAD patients who do not display any circadian abnormalities, so other mechanisms may also be involved in the pathogenesis of SAD.

There is converging evidence that alteration of monoaminergic neurotransmitters, such as serotonin, norepinephrine, or even dopamine, may be involved in the pathophysiology of SAD. Tryptophan depletion has been used to selectively reduce the plasma tryptophan concentration by administration of a mixture of amino acids free of tryptophan, which is a precursor of serotonin. Studies using neuroimaging techniques have been able to show that serotonin synthesis is reduced for a few hours in the human brain after this procedure. Additionally, two further studies have demonstrated that SAD patients in stable remission during summer time and after successful BLT experience a temporary depressive relapse after tryptophan depletion. To investigate the role of norepinephrine in SAD, Neumeister et al conducted a study comparing the effects of tryptophan depletion with catecholamine depletion and sham depletion in SAD patients in remission with BLT. Both active depletion protocols resulted in temporary depressive relapses providing evidence that brain catecholaminergic systems may also be involved in the mechanism of action of BLT. Interestingly, another study in SAD was able to demonstrate that monoamine depletion led to alterations in several humor and cellular immunologic parameters, suggesting a potential role of the immune system in the pathogenesis of the disorder.

Several neuroimaging studies have investigated the importance of specific molecular targets in the pathophysiology of SAD. Binding studies using 123I-CIT and single photon emission computed tomography (SPECT) have found that depression in SAD is associated with reduced serotonin transporter availability in the thalamus and hypothalamic regions. A further study was likewise able to show reductions in the availability of striatal dopamine transporter binding sites in untreated depressed SAD patients. This study provides evidence that the dopaminergic systems may also be involved in the pathogenesis of SAD. However, these findings do not explain whether lowered availability of monoamine transporters in the synaptic cleft represents a primary defect or an attempt to overcome a state of possible lowered dopamine-serotonin availability during a depressive episode.

There is evidence that specific genetic factors may lead to increased vulnerability for developing SAD. Genetic association studies have examined the role of several candidate genes: a number of surveys have investigated the serotonin transporter promoter repeat length polymorphism (5-HTTLPR), but the results of these studies are inconsistent. One study examined the relationship between SAD and PMDD and found an association between the presence of PMDD and family history and 5-HTTLPR long/short allele-heterozygosity in females with SAD. PMDD and SAD may thus share some genetic vulnerability factors such as the 5-HTTLPR. A higher rate of affective disorders in relatives of patients with SAD and PMDD may be indicative of higher genetic vulnerability in this subgroup when compared with patients with SAD alone. A further interest-deserving study investigated the association of the 5-HTTLPR with the DSM-IV clinical subtypes of depression: Wilkeit et al were able to demonstrate that melancholic depression is associated with the 5-HTTLPR long allele and atypical depression with the short allele.

Apart from the 5-HTTLPR several other candidate genes have been investigated: guanine nucleotide-binding proteins (G-proteins) have been implicated in affective disorders, with reports of altered signal transduction and G-protein levels. There is evidence that specific genetic factors may be involved in the pathogenesis of SAD. However, these findings do not explain whether lowered availability of monoamine transporters in the synaptic cleft represents a primary defect or an attempt to overcome a state of possible lowered dopamine-serotonin availability during a depressive episode.

Apart from the 5-HTTLPR several other candidate genes have been investigated: guanine nucleotide-binding proteins (G-proteins) have been implicated in affective disorders, with reports of altered signal transduction and G-protein levels. There is converging evidence that alteration of monoaminergic neurotransmitters, such as serotonin, norepinephrine, or even dopamine, may be involved in the pathophysiology of SAD. Tryptophan depletion has been used to selectively reduce the plasma tryptophan concentration by administration of a mixture of amino acids free of tryptophan, which is a precursor of serotonin. Studies using neuroimaging techniques have been able to show that serotonin synthesis is reduced for a few hours in the human brain after this procedure. Additionally, two further studies have demonstrated that SAD patients in stable remission during summer time and after successful BLT experience a temporary depressive relapse after tryptophan depletion. To investigate the role of norepinephrine in SAD, Neumeister et al conducted a study comparing the effects of tryptophan depletion with catecholamine depletion and sham depletion in SAD patients in remission with BLT. Both active depletion protocols resulted in temporary depressive relapses providing evidence that brain catecholaminergic systems may also be involved in the mechanism of action of BLT. Interestingly, another study in SAD was able to demonstrate that monoamine depletion led to alterations in several humor and cellular immunologic parameters, suggesting a potential role of the immune system in the pathogenesis of the disorder. Several neuroimaging studies have investigated the importance of specific molecular targets in the pathophysiology of SAD. Binding studies using 123I-CIT and single photon emission computed tomography (SPECT) have found that depression in SAD is associated with reduced serotonin transporter availability in the thalamus and hypothalamic regions.
knowledged BLT as the first-line treatment for SAD (Table IV). Light boxes emitting full-spectrum bright white light of an intensity of 2500 to 10 000 lux in a distance of 60 to 80 cm have been most frequently used for BLT. Patients have to be instructed to use BLT for half to 1 hour on a daily basis during the whole fall and winter season. The duration of treatment can be gradually increased to 2 hours and more per day in case of partial or insufficient response. It has been demonstrated that the antidepressant effect of BLT is higher when it is used in the morning.60,61 BLT has a very high acceptance among patients; side effects are mostly mild and transient and rarely lead to discontinuation of therapy (Table V).62-67 The combination of BLT with other nonpharmacological treatment approaches, such as therapeutic sleep deprivation,68 has been recommended to increase its efficacy. In spite of the significance of BLT, it is also important to recognize the limitations: Pjrek et al69 reviewed the clinical course of 553 SAD patients and found that only about half of them were sufficiently treated with BLT as monotherapy. Forty-nine percent of patients in this study received psychopharmacological medication and 35.4% had to be treated with antidepressants in addition to BLT.

Despite the clinical importance of antidepressants and in contrast to the numerous reports of BLT, there have been relatively few studies on the efficacy of psychopharmacological medication for SAD.70-72 To our knowledge, there is only one placebo-controlled trial on the selective serotonin reuptake inhibitor (SSRI) sertraline72 that has been able to successfully confirm the superiority of the compound in comparison with placebo. Other studies, like the study of Lam et al73 on fluoxetine or that of Lingjaerde et al74 on moclобemide have shown a higher rate of responders or more rapid remission of atypical symptoms, respectively. However, these results are not statistically significant due to small sample sizes and a very high rate of placebo responders, which is a common methodological issue in samples mostly consisting of patients with mild-to-moderate depression. Besides, there have been several case reports and open studies investigating the usefulness of different antidepressant drugs, eg, citalopram,75 Hypericum extract,76,77 mirtazapine,78 and reboxetine.79 Table VI80 summarizes potential indications for pharmacological treatment of SAD.

While there is at least a scientific basis for the treatment of SAD with a unipolar course of illness, a search of the available literature reveals a lack of studies on specific psychopharmacological treatment for bipolar SAD. Furthermore, few bipolar SAD patients are willing to accept treatment with phase prophylactic medication.80 However, in the absence of controlled trials it seems reasonable to adapt guidelines for the treatment of nonseasonal bipolar affective disorder81,82 for bipolar SAD.

Recently, there have been reports on the use of transcranial magnetic stimulation (TMS) in patients with SAD.83 While these preliminary data suggest that TMS is effective and lacks major side effects, future studies have to evaluate the importance of this method in the clinical management of SAD.

### Conclusions

SAD is a rather frequent psychiatric disorder in the general population, but it is inadequately identified, with a diagnostic latency of about 10 years after the first depressive episode. Besides, seasonal changes in mood also impair social functioning and

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<th>Common side effects62-63</th>
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<tr>
<td>- Headache</td>
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<td>- Eye strain, vision problems</td>
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<td>- Insomnia</td>
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<td>- Irritability</td>
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<td>- Agitation, restlessness</td>
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<td>- Nausea</td>
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<td>- Photophobia</td>
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<th>Rare side effects (casuistic reports)</th>
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<tr>
<td>- Hyponmania64</td>
</tr>
<tr>
<td>- Suicidal ideations65</td>
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<tr>
<td>- Menstrual disturbances66</td>
</tr>
<tr>
<td>- Retinal damage? (no certain proof until now)67</td>
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<tr>
<th>Prior positive response to antidepressants or mood stabilizers</th>
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<th>Bipolar disorder (phase prophylaxis, treatment of acute manic or hypomanic episodes)</th>
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<th>Melancholic features specifier (predicts non-response to bright light therapy [BLT]68)</th>
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<th>Severe subtypes of depression (eg, psychotic)</th>
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<th>History of recurrent depression in the moderate-to-severe range (need for psychopharmacologic long-term treatment?)</th>
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<th>High suicide risk (assess the need for hospitalization, avoid tricyclic antidepressants to prevent overdose)</th>
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<th>Marked impairment in occupational functioning, in usual social activities, or in relationships with others</th>
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<th>Patient preference</th>
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<th>Intolerable side effects of BLT</th>
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Table IV. Guidelines for the use of bright light therapy (BLT) for seasonal depression.

Table V. Adverse effects associated with bright light therapy.62-67

Table VI. Indications for pharmacotherapy in patients with seasonal affective disorder (SAD).
reduce patients’ performance at work. In SAD, in its most frequent manifestation, fall-winter depression, is characterized in most cases by reverse vegetative symptoms such as increased appetite, carbohydrate craving, hyperosomnia, daytime fatigue, and loss of energy. However, the most important clinical feature is that patients feel worst in the fall-winter months, ie, in the time of light deficiency. Changes in hormonal and monoaminergic neurotransmitter function as well as an underlying genetic predisposition have been implicated in the pathogenesis of SAD. Antidepressant psychopharmacotherapy is used for the treatment of SAD depression similar to other forms of depression; however, BLT is now recognized as the treatment option of choice. Future research should aim at investigating specific treatment options for SAD patients with a bipolar course of illness.

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Seasonal affective disorder: from diagnosis to treatment – Winkler and Kasper

TROUBLE AFFECTIF SAISONNIER : DU DIAGNOSTIC AU TRAITEMENT

Le trouble affectif saisonnier (TAS, ou « blues de l’hiver ») est un sous-type de la dépression majeure ou du trouble bipolaire qui fait l’objet de recherches en psychiatrie depuis plus de 20 ans. La prévalence dans la population générale varie entre 2 % et 5 % dans les pays à climat tempéré, les femmes étant beaucoup plus souvent touchées par le syndrome. Des symptômes dépressifs atypiques accompagnés d’une symptomatologie végétative inversee prédominent pendant les épisodes dépressifs au cours de la période obscure de l’année, tandis qu’un quart des patients environ présentant des épisodes hypomaniaques (rarement maniaques) pendant la période printemps/été. La lumi-nothérapie est généralement admise comme traitement de la dépression du TAS, mais le traitement psychopharmacologique par les antidépresseurs s’est également révélé efficace et bien toléré. Il est à noter que plusieurs concepts physiopathologiques sont les plus importants et donnent un aperçu des méthodes diagnostiques actuelles ainsi que des options thérapeutiques pour les TAS.

Trends in diagnosis and treatment of bipolar disorders

by D. J. Kupfer and E. Frank, USA

Bipolar disorder (manic-depressive illness) is a chronically recurring subtype of mood disorders that is associated with considerable psychiatric and medical comorbidity. Psychiatric comorbidity, such as alcohol or drug abuse, anxiety, and panic disorder adversely influences outcomes. Medical disease and medical risk factors are common in bipolar disorder and lead to even greater morbidity and mortality in this population. Associated with a high rate of suicide, bipolar disorder is a potentially lethal disease. In considering appropriate interventions for bipolar disorder, it is easiest to group them as treatment of acute mania or mixed states, treatment of acute depression, and treatment for the prevention of both manic and depressive recurrence. Monotherapy, usually in the form of lithium, valproate, or one of the atypical antipsychotic medications, is initially recommended for the treatment of mania and mixed states. The treatment of acute depression is generally longer and more difficult than mania. Many expert clinicians have recommended optimization of a mood stabilizer and, if this strategy is ineffective, adding an antidepressant to the mood stabilizer. Mood stabilizer monotherapy was once considered the ideal maintenance treatment; however, considerable attention has now been devoted to the conduct of controlled trials of atypical antipsychotic medications in the maintenance phase. In considering future trends, the increased use of atypical antipsychotics and their possible efficacy, not only for stabilization of mania, but for depressive symptomatology, is an important area of further investigation. Furthermore, the use of agents with a regulatory effect on biological rhythms deserves further exploration.

Keywords: bipolar disorder; atypical antipsychotic; mania; depression; maintenance treatment

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Another major feature of bipolar disorder is the level of psychiatric and medical comorbidity. Community-based studies indicate that 60% to 70% of individuals with bipolar illness meet diagnostic criteria for a lifetime history of substance abuse or dependence. The risk for alcohol or drug abuse is 6 to 7 times greater in patients with bipolar disorder than would be expected in the general population.5 A more recent investigation from the Stanley Foundation Bipolar Network reports 2 to 3 times the population rate of alcohol abuse in men with bipolar disorder and 7 times the frequency in women.6

Among other psychiatric comorbidities, anxiety, panic disorder, and panic spectrum disorder are common and adversely influence bipolar outcomes. Angst and colleagues have reported that the association with panic is greater in patients with bipolar disorder than in patients with major depression (J. Angst, personal communication). Panic and other forms of anxiety significantly delay remission of acute bipolar episodes.7,8 The presence of somatic symptoms in bipolar disorder, particularly cardiovascular symptoms, is increased in the presence of panic disorder. McElroy and colleagues9 have highlighted the frequency of eating problems in bipolar disorder, including symptoms of bulimia nervosa and, in particular, binge eating.

Associated with a high rate of suicide, bipolar disorder is a potentially lethal disease.10,11,12 Medical disease and medical risk factors are present in bipolar disorder and lead to even greater morbidity and mortality in this population. The most commonly reported problems are cardiovascular disease, diabetes, obesity, and thyroid disease. The most common medical risk factors related to excessive nicotine use, alcohol and drug use, concomitant anxiety, and eating disorders, lead to the early onset of medical diseases with poor long-term outcomes. Furthermore, because patients with bipolar disorder spend most of their time in the depressive phase of the illness, there is often a loss of the discipline and motivation required to reduce such medical risk factors. Katon12 has established the clear relationship between depression and a host of negative health behaviors including smoking, poor diet, overeating, and sedentary lifestyle and has shown that depression has a maladaptive effect on adherence to medical regimens and direct adverse physiological effects including decreased heart rate variability and increased adhesiveness of platelets.

Bipolar I disorder is almost always treated in mental health settings, with patients viewing their psychiatric care as their most important form of medical care. This has led to a relative underrecognition of and inattention to the many physical diseases from which these patients suffer. Only recently has there been a greater awareness of medical burden and medical risk factors, stimulated by the introduction of atypical antipsychotic medication for bipolar I disorder with its attendant medical problems, led clinicians and investigators to focus on these issues. Today there is broad recognition that advances in the treatment of bipolar disorder must go together with increased medical risk factor assessment, ongoing laboratory surveillance, and integrated treatment intervention. As highlighted recently,13 progress has been made in understanding the role of genetics in bipolar disorder and complemented by findings from the neuroimaging field, both functional magnetic resonance imaging (fMRI) and structural imaging. First, studies repeatedly confirm that bipolar disorder has extremely high heritability.14 Second, they demonstrate increased frequency of bipolar disorder in family members, but also of other disorders that are primarily psychotic disorders (schizoaffective disorder and schizophrenia).15 Specific chromosomal regions have been identified, but only 5 out of 16 chromosomal regions currently meet criteria for significant linkage.14 Complementing this work on genetics, anatomical and MRI neuroimaging studies have demonstrated functional abnormalities of the medial prefrontal cortex.16 Neurocognitive dysfunction, including abnormalities in cognitive and memory activity,17,18 but particularly in social cognition,19 have been found in individuals with bipolar disorder. This is consistent with work of others, including Phillips,20 who has been particularly interested in alterations in emotional perception. Neurocognitive deficits and, perhaps, deficits in social cognition may represent, if not specific, at least consistent findings in bipolar...
Trends in diagnosis and treatment of bipolar disorders – Kupfer and Frank

Once thought of as our “good prognosis” illness in psychiatry, bipolar disorder has emerged in the last decade as one of our most significant treatment challenges. Thinking back to what it must have been like to try to manage this condition in the pre-lithium era, it is easy to understand how, once lithium was introduced, the field was lulled into a false sense of complacency. In the late 1980s and early 1990s, however, both naturalistic data\(^2,28\) and data from controlled trials (eg, Prien et al,\(^2,29\) 1984) made it clear that bipolar disorder was not a problem solved. This led a relatively small group of investigators in the US and abroad to take a renewed interest in developing treatment strategies for bipolar disorder, both psychopharmacologic and psychotherapeutic.\(^30\) As we have entered the 21st century, we have come to recognize the multiple factors that complicate the process of achieving ideal outcomes for those that suffer from bipolar disorder.

Our model for understanding these complexities is illustrated in Figure 3. According to our model, the early age of onset typical of bipolar disorder means that early years spent in coping with the illness often lead to social developmental/maturational deficits. Future experience of the illness often, then, takes place against a background of such deficits.

**Psychiatric comorbidity**
- Panic
- Ethyl alcohol
- Substance disorders
- Personality disorders

**Psychotic symptoms**
- Delusions
- Hallucinations

**Manic mood and behavior**
- Euphoria
- Grandiosity
- Pressured speech
- Impulsivity
- Excessive libido
- Recklessness
- Intrusiveness
- Reduced need for sleep

**Medical comorbidity**
- Obesity
- Thyroid disease
- Diabetes
- Cardiovascular

**Cognitive symptoms**
- Racing thoughts
- Anxiety
- Distractibility
- Disorganization
- Inattention

**Array of bipolar disorder symptoms**

**Poor treatment adherence**

**Early onset of illness**

**Background of social developmental/maturational deficits**

**Psychotic or negative mood and behavior**
- Depression
- Anxiety
- Irritability
- Hostility
- Violence or suicide

**Limited educational attainment**

**Unemployment and poverty**

Figure 3. A model of intervention points for improving treatment outcomes in bipolar disorder.

**Treatment paradigms in bipolar disorder**

Once thought of as our “good prognosis” illness in psychiatry, bipolar disorder has emerged in the last decade as one of our most significant treatment challenges. Thinking back to what it must have been like to try to manage this condition in the pre-lithium era, it is easy to understand how, once lithium was introduced, the field was lulled into a false sense of complacency. In the late 1980s and early 1990s, however, both naturalistic data\(^2,28\) and data from controlled trials (eg, Prien et al,\(^2,29\) 1984) made it clear that bipolar disorder was not a problem solved. This led a relatively small group of investigators in the US and abroad to take a renewed interest in developing treatment strategies for bipolar disorder, both psychopharmacologic and psychotherapeutic.\(^25\) As we have entered the 21st century, we have come to recognize the multiple factors that complicate the process of achieving ideal outcomes for those that suffer from bipolar disorder.

Our model for understanding these complexities is illustrated in Figure 3. According to our model, the early age of onset typical of bipolar disorder means that early years spent in coping with the illness often lead to social developmental/maturational deficits. Future experience of the illness often, then, takes place against a background of such deficits.
cits making rational decision-making and coping with difficult challenges more difficult for the individual even during euthymic periods. The complexity of the disorder itself (as discussed earlier), involving as it does an ever-changing mix of psychotic symptoms, dysphoric or negative mood and behavior, manic mood and behavior, and cognitive symptoms makes treatment decision-making a constantly ongoing process in which no sooner is a symptom or group of symptoms effectively addressed than others appear which require new treatment decisions. Further complicating the picture are the psychiatric and medical comorbidities commonly encountered in bipolar disorder: panic, alcohol abuse, substance abuse, and personality disorders (particularly Cluster B disorders) as well as obesity, thyroid disease, diabetes, and cardiovascular disease. Each of these comorbidities can have important impact on treatment decisions. For example, we have observed that patients with panic comorbidity are much more sensitive to medication side effects, often necessitating slower starting doses and slower titration of new treatments. In the area of medical comorbidity, those patients with thyroid disease or diabetes also warrant special clinical attention if their bipolar disorder treatment is to be benign with respect to these medical conditions. Finally, although treatment adherence is an issue in all of medicine, it seems to be a particular challenge for patients with bipolar disorder. As Figure 3 illustrates, multiple factors in the model including the poor judgment brought on by mania or substance use, the medication sensitivity brought on by panic comorbidity, and the desire to limit weight gain in an already obese individual, may all contribute to the challenges to treatment adherence in this population. Thought of in this way, there are, then, a series of potential targets for improving treatment paradigms for bipolar disorder.

In considering appropriate interventions for bipolar disorder, it is easiest to group them as treatment of acute mania or mixed states, the treatment of acute depression, and the treatment for the prevention or prophylaxis of both mania and depression in the future (maintenance treatment). The treatment of acute mania involves the following aims: the improvement of manic symptoms, possibly requiring rapid tranquilization; the resolution of manic symptomatology avoiding both the onset of new depressive symptomatology or the unmasking of depressive symptomatology; and finally, the consideration of mood stabilization and subsequent treatment. With respect to rapid tranquilization, Cookson and others have demonstrated that haloperidol, as well as the new atypical antipsychotics, have immediate antimanic effects independent of sedation. Other drugs often used in the treatment of acute mania may not act as quickly and therefore have delayed antimanic effects. The American Psychiatric Association (APA) Guidelines suggest that for mild mania, lithium or valproate or an atypical antipsychotic can be utilized; for more severe mania, atypical antipsychotics or valproate are recommended. For mania associated with psychosis, atypical antipsychotics are preferred.

Monotherapy is initially recommended to address manic features. The use of lithium, valproate, as well as of a number of atypical antipsychotics, including olanzapine, risperidone, quetiapine, nefazodone, and aripiprazole is recommended. If patients do not improve on any of these drugs, a number of clinical specialists have suggested that the addition of olanzapine, risperidone, or quetiapine to lithium or valproate confers an additional effect, as does the addition of valproate. The avoidance of major depressive symptomatology as an outcome in the successful resolution of manic symptoms could be helped by use of antipsychotics, which may have antidepressant effects of their own. It is further recommended that after acute treatment, on the way to stabilization and maintenance treatment, patients and family members receive psychoeducation, with particular emphasis on recognition of early symptoms of mania. Many clinicians also further recommend the availability of rescue medication, such as small doses of an atypical antipsychotic.

The treatment of acute depression is longer and more difficult than that of mania, as shown in Figure 4. Many expert clinicians have recommended the initial optimization of a mood stabilizer and, if this strategy is ineffective, adding an antidepressant to the mood stabilizer. If this second step does not work, then there are a variety of recommendations including adding a second mood stabilizer. Recently, it has been shown that an atypical antipsychotic plus an selective serotonin reuptake inhib-
Unmet Needs in the Treatment of Depression

Lithium appears to be effective for the prevention of manic episodes, have the following information: lithium appears to possess antidepressant efficacy in acute bipolar depression. Recent reviews of controlled trials of antidepressants versus placebo have demonstrated a mild positive effect for antidepressants, accomplished by a relatively low switch rate from depression to mania with antidepressants (except for the tricycles). Two clinical trials with quetiapine have shown efficacy in acute bipolar depression (J. R. Calabrese, personal communication). The failure to respond to a mood stabilizer (or an atypical antipsychotic) with or without an antidepressant leads the clinician to consider substituting another antidepressant or mood stabilizer, as well as the use of electroconvulsive therapy (ECT) and/or adjunctive psychological interventions. Finally, a key unanswered question is how long one should continue an antidepressant following resolution of a bipolar depressive episode. No guidelines, similar to those available for the treatment of acute unipolar depression, exist.

When we review options for long-term treatment, one important issue is that we need to deal with the prevention of both manic and depressive episodes. Indeed, one could list the therapeutic objectives in the following manner: to achieve symptom control of all four domains that have been mentioned previously; to prevent syndromal recurrence; and to reduce or obliterate all subsyndromal symptomatology because this is often related to significant functional impairment. Finally, it is important to minimize the risk of cycling, which, when it occurs, makes it more difficult to treat both the acute manic or depressive state and to manage the illness over the long term.

Complicating the treatment of bipolar disorder, both acutely and long term, is the presence of considerable psychiatric and medical comorbidity. Therefore, a successful long-term treatment approach will also assist in treating the psychiatric and medical comorbidities. Underscoring the importance of complete symptomatic relief is the associated functional recovery as manifested by return to work, family, and schooling for younger people.

Another important consideration in maintenance treatment is a reduction in overall mortality. While a great deal of appropriate attention has been devoted to suicide prevention, bipolar patients also die of other causes, especially medical disease. Consequently, a major goal of maintenance treatment is to reduce overall mortality. This goal is complicated by the fact that adherence to treatments for both medical and psychiatric disorders for patients with bipolar disorder is very poor and, therefore, we must pay specific attention to treatment adherence principles.

In reviewing the possibilities of long-term treatment in bipolar disorder, at the present time we have the following information: lithium appears to be effective for the prevention of manic episodes, but not necessarily depressive episodes, the data for valproate for long-term treatment are minimal despite its wide use; the data for lamotrigine for long-term treatment support a specific indication for the prevention of depressive as compared with manic episodes. Recently, attention has been devoted to the conduct of controlled trials of atypical antipsychotics in the maintenance phase. The majority of such controlled studies have been carried out with olanzapine, with one recent trial of aripiprazole. Studies of olanzapine demonstrate superior efficacy to valproate; and comparisons of olanzapine to lithium show an advantage of olanzapine with respect to study completion. An olanzapine versus placebo study for relapse prevention demonstrated efficacy for olanzapine in preventing relapse into mania as well as into depression. Finally, a study comparing olanzapine plus lithium or valproate versus placebo plus lithium or valproate showed the advantage of the addition of olanzapine as compared with placebo, suggesting the possibility of combined long-term treatment. Recently, a 26-week trial comparing aripiprazole to placebo has been reported demonstrating a significant advantage for this atypical antipsychotic.

Maintenance treatment should include, at the minimum, patient management strategies consisting of five specific areas: establishment and maintenance of a therapeutic alliance; education of patients and their families about the disorder; efforts to enhance treatment adherence; promotion of awareness of stresses, sleep disturbance, and early signs of relapse and regular patterns of activity; and finally, evaluation and management of functional impairment. Furthermore, targeted psychosocial interventions are now being studied in the treatment of bipolar disorder that may be very applicable to larger groups of patients suffering from this illness. Interestingly, these approaches generally include strong emphasis on improving treatment adherence.

Future trends

In considering future trends, the increased use of atypical antipsychotics and their possible utility, not only for stabilization of mania, but for depressive symptomatology, is an important area of further investigation. That monotherapy may not be the optimal way to proceed with patients with bipolar disorder is becoming clearer, making it very likely that an increased emphasis will be placed on combination treatments in the next 5 years. It is hoped that controlled clinical trials will be available to guide the clinician. With respect to the treatments specifically for bipolar depression, it is likely that a novel serotonin receptor agonist or antagonist will be used to treat bipolar depression. Some of the other novel treatments being suggested for unipolar depression may also be useful for bipolar depression. In assessing the risk-benefit ratio of the use of any medication in bipolar disorder, it is important to consider the level of medical risk factors that may make patients more vulnerable to the adverse effects of certain atypical antipsychotics and to the development of increased suicidality.
oment of medical diseases. Consequently, patients with bipolar disorder should receive careful medical monitoring throughout the period of treatment. While we have considered the need for new drug treatment targets, it is also clear that our understanding of bipolar disorder will also be facilitated by paying more careful attention to a better definition of behavioral phenotypes as well as to identifying markers for intermediate endophenotypes. This will require the use of pharmacogenomic strategies, neuroimaging techniques, the application of social rhythm and social cognition strategies, as well as further examinations of temperament. Only by defining better phenotypes and endophenotypes, will we be able to understand the pathogenesis of bipolar disorder.

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**DIAGNOSTIC ET TRAITEMENT DES TROUBLES BIPOLAIRES : TENDANCES ACTUELLES**

*Le trouble bipolaire (psychose maniacodépressive) est un sous-type des troubles de l’humeur chroniquement récurrent associé à une considérable comorbidité psychiatrique et médicale. La comorbidité psychiatrique, telle que l’abus d’alcool ou autres substances, l’anxiété et les troubles paniques influent défavorablement sur l’évolution. Une affection médicale et des facteurs de risque médicaux sont fréquents au cours des troubles bipolaires et conduisent à une morbidité et une mortalité encore plus importantes dans cette population. Associé à un taux élevé de suicide, le trouble bipolaire est une maladie potentiellement létale. À la lumière des attitudes thérapeutiques adaptées aux troubles bipolaires, il est plus facile de les regrouper en traitement pour les états maniaques ou mixtes aigus, traitement de la dépression aiguë et traitement préventif de la récurrence dépressive et maniaque. La monothérapie, habituellement administrée sous la forme de lithium, de valproate ou d’un médicament antipsychotique atypique, est recommandée dans un premier temps pour le traitement des états maniaques et mixtes. Le traitement de la dépression aiguë est généralement plus long et plus difficile que celui des états maniaques. De nombreux cliniciens experts ont recommandé l’utilisation optimisée d’un régulateur de l’humeur et, si cette stratégie n’est pas efficace, l’association d’un antidépresseur au régulateur de l’humeur. La monothérapie par régulateur de l’humeur était considérée autrefois comme le traitement d’entretien idéal ; toutefois, l’intérêt se porte désormais de plus en plus sur des études contrôlées de médicaments antipsychotiques atypiques dans la phase d’entretien. L’utilisation croissante des antipsychotiques atypiques et leur possible efficacité, non seulement pour stabiliser les états maniaques, mais aussi pour la symptomatologie dépressive, constitue un important champ d’investigation pour les orientations ultérieures. Enfin, l’utilisation d’agents ayant une action régulatrice sur les rythmes biologiques mérite d’être explorée plus avant.*
What are the core symptoms of depression?

1. M. P. Deva, Brunei

The problem with core symptoms is the availability of acceptable guidelines and classifications of depressive illnesses. Many nonpsychiatrist doctors consider any patient who is distressed as depressed, especially if the patient is crying! Suicide attempts or parasuicides are always equated by nonpsychiatrists as depression. Persons who are irritable and angry and easily provoked are often seen as either normal or psychotic, but seldom considered to be depressed. Such looseness in diagnosis leads to injudicious use and noneffectiveness of antidepressant medicines. Thus, a review of the current concepts in recognizing depressive illnesses and treating them is needed. The answer lies in a good history taking through a good interview of the patient. The core symptoms include a history of at least 3 weeks (but usually 6 weeks) of low mood and negative thoughts, gloomy outlook on everyday topics, sleep patterns disturbed without reason, lack of interest in eating, some loss of weight, poor interest in work, recreation, sexual function. To patients, everything looks gray, hopeless, useless, they have vague thoughts of leaving their job, going somewhere else, or even “ending it all.”

2. T. Partonen, Finland

Depression is heterogeneous in terms of etiology and phenotype. Depressions are many; they vary according to profile and intensity of symptoms, and course and cause of illness. Symptoms may be melancholic, atypical, psychotic, or mild; there may be one or numerous episodes; the course may be recurrent or chronic; the depression may be reactive or endogenous in nature. Thus, trying to pin down the core of depression is like peeling an onion. The essential characteristic of depression is the feeling of loss: the core symptoms of depressive disorder are therefore lack of pleasure and sadness, in other words, anhedonia and depressed mood. These constitute the key criteria for a major depressive episode, not only in terms of diagnosis, but also of evolution. However, this point of view has been challenged by recent findings suggesting a need to focus on core pathways in the pathogenesis of illness rather than on manifestations of individual disorders. Several arguments can be put forward in favor of this. For instance, depressive disorders and generalized anxiety disorder tend to be related to the same genetic factors and may be interpreted as different manifestations of the same predisposition. This predisposition could involve mutations in the so-called circadian clock genes and result in errors in regulation of the circadian pacemaker. This would lead to abnormal circadian rhythms and alteration of the sleep-wake cycle, resulting in changes in core body temperature and short latencies to rapid eye movement (REM) sleep, the outcome of which is compromised mood regulation and ultimately, feelings of depression and anxiety. One way to look at the question is to analyze the individual domains that may show differing trajectories rather than the overall severity of depression reflecting a summation of these domains. Severe depressions are characterized by two symptoms only that commonly occur in both typical and atypical depressive disorders. These key symptoms—

Core symptoms of depressive illnesses
Depression is characterized by the following symptoms, whether in developing countries or in other countries.

- Lowering of mood, volition and outlook. The patient has a negative outlook, a low mood, a feeling of loss, of despondency. Everything is colorless, negative, gray, and gloomy.
- Inability to deal with normal work, play, and social obligations satisfactorily.
- Preoccupation with bodily functions and physical symptoms. Patients often want their doctor to prove they have a physical disease that is not there.
- Sleep disturbances. Patients usually report early morning awakening, but many experience difficulty in falling asleep.
- Disturbances in eating. Patients show a lack of interest in food and therefore usually lose weight; occasionally, they eat too much and put on weight.
- In severe and prolonged depressive illnesses there may be suicidal ideas, a stuporous state.

What are the core symptoms of depression?
feelings of depression and loss of interest—are reported by 9 patients out of 10. Are these the core symptoms of depression? Not necessarily, since in addition to these two symptoms, severe typical depression is characterized by difficulty in concentrating, insomnia, and loss of pleasure. Moreover, major depressive episodes with a seasonal pattern (seasonal affective disorder) are frequently accompanied by atypical symptoms of depression such as prolonged sleep, weight gain, carbohydrate craving, and increased appetite. Nevertheless, a simple two-question screening tool inquiring about the presence of depressed mood and anhedonia may just be as effective as a more complex questionnaire. Despite its limitations, such a screening tool is certainly a useful, more pragmatic, and less time-consuming method for detecting depression in the primary care setting. Specific groups of individuals with depressive disorder, including children and adolescents, women after delivery, and the elderly, need specific attention in clinical practice, since their clinical picture may differ, and therefore can be missed by the usual case-finding instruments, thereby depriving scores on the routinely administered rating scales. For example, depressive elderly persons with mild cognitive impairment tend to report sadness, anhedonia, and pessimistic thoughts. Self-reports of depression may be of benefit in terms of both expense and time, and a valuable substitute for clinician-based ratings in treatment trials of outpatients with major depressive disorder, but no psychotic symptoms or cognitive impairment. Global ratings, however, seem to produce less valid findings than specific item-based ratings. To ensure optimal control of the core symptoms of depression, an antidepressant should have mood-lifting and energizing effects, in other words it needs to achieve elation and activation. Rapid relief from anxiety and insomnia are naturally of great help for a good outcome. In the long run, the patient will recover feelings of pleasure and optimistic thoughts. However, it is necessary to realize that no treatment—not even the most potent one—stands a true chance of success if resources in terms of health-care professionals are insufficient to ensure an adequate follow-up of patients suffering from depression.
Depression has been a long-standing focus of attention for writers, poets, philosophers, artists, and, eventually, scientists. The theories proposed to explain depression have shed light on the many facets of the disease and contributed to increase our awareness, understanding, and conceptualization of it. Thus, Freud stressed the importance of grieving in depression, in the absence of any obvious loss. Beck, a psychoanalyst and the father of the Depression Inventory that bears his name, started investigating the role of aggression directed toward self in depression, and ended up by formulating a cognitive theory of depression. Interestingly, almost all theories have emphasized two symptoms of depression; depressed mood and anhedonia/loss of interest. These symptoms are also included in the core of Hamilton’s conceptualization of depression as presented in the Hamilton Depression Rating Scale. Eventually, the Diagnostic and Statistical Manual of Mental Disorders (DSM) approach highlighted depressed mood and anhedonia/loss of interest as the cardinal features of depression. Since the third edition of the DSM in 1980, the differences among cultures have gradually subsided, mainly due to the widespread acceptance of the conceptual framework enshrined in the DSM classification system. Recent studies indicate that, although culture can affect the expression of depressive mood and symptoms, there appears to be a “core syndrome” of depression, regardless of sociocultural context. Current classification systems consider depressed mood and anhedonia/loss of interest as the “core” symptoms of depression. Classification systems relying on clinical presentation need to identify “core” symptoms to differentiate individual “disorders,” which are accordingly defined. However, major drawbacks are associated with the DSM approach regarding the conceptualization of depression, and, as the etiopathology of depressive disorders is increasingly elucidated, the concept of “core” symptoms tends to be replaced with etiologically relevant symptom profiles. First of all, the DSM approach relies heavily on “clinical” observations, and in terms of etiology—the ultimate goal of any classification—this hardly allows to go beyond syndrome level. Secondly, the description of depression is best adapted to middle-aged patients without comorbid psychiatric or physical disorders. Even when only anxiety disorders are taken into account, at least 50% of depressive patients present with symptoms of anxiety that interact with the symptomatology produced by depression. Last but not least, in describing a common “major depressive episode” syndrome, the DSM emphasizes similarities more than differences among disorders, thus decreasing the possibility of detecting differences in underlying etiopathology. In all, the drawbacks of the DSM system restrict the number and power of the studies investigating the heterogeneity of depressive disorders. All symptoms are the end-product or by-product of pathological or functional changes in organs. The brain is an organ with highly specialized functions assigned to different areas of the hemispheres. Unlike most other organs, expansion or a slight change in the location of pathology can result in very different clinical presentations. In regard to depression, great variability of symptoms and high frequency of comorbid diseases could well be related to the extent of the areas affected. To date, although much remains to be learned, we do have some clues about the possible brain locations that control some of functions that are affected in depression. For example, depressed mood possibly originates in increased activity of the limbic cortex, specifically, the anterior cingulate cortex and the limbic orbital cortex. Abnormal neuronal activity in the hypothalamus and other limbic areas could lead to anhedonia/loss of interest, decreased libido, and dysregulation of appetite and sleep. We also know some of the areas involved in other psychiatric disorders as well. For example, the hippocampal region is affected in dementia, and mesolimbocortical dopaminergic pathways and the prefrontal cortex are affected in schizophrenia. I fully expect that, in future, new syndromes will be defined according to the affected brain areas and circuits, and that this will lead to a thorough overhaul of current diagnostic criteria for psychiatric disorders. In conclusion, although we still need to rely on “core” and other symptoms for the differential diagnosis of depression, we should also bear in mind that the current conceptualization of depression limits our understanding of depression and how to treat it. Once the diagnosis of depression has been established, all the symptoms and signs presented by the patient should be considered as “core” symptoms. Every single symptom should receive clinical attention regardless of severity. We should rethink our current partially successful concept of medical treatment that considers depression as a whole. Instead, we should focus on individual symptoms and new therapeutic strategies to address them.

REFERENCES
It is well known that the word depression refers both to a full-fledged clinical condition and to brief, mild downward mood swings that we all experience as a part of daily living. In the clinical context, the term depression refers not simply to a state of depressed mood, but to a syndrome comprising mood disorders, psychomotor changes, and various types of somatic (neurovegetative) dysfunction and cognitive impairment. According to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), all these changes may occur (they should be present for at least 2 weeks), but none except “depressed mood” and “loss of interest or pleasure in nearly all activities,” are essential for the diagnosis of Major Depression. DSM-IV and the International Statistical Classification of Diseases and Health-Related Problems, 10th Revision (ICD-10) show some degree of divergence in their criteria for depression, regarding type and number of symptoms. ICD-10 contains 10 items, in contrast to the 9 DSM-IV items (loss of self-esteem is in a separate category from inappropriate guilt in ICD-10). Also, in ICD-10, the severity of Major Depressive Episodes is rated according to an incremental number of criteria: mild depression starts from 4 out of 10 symptoms, moderate depression from 6 out of 10 symptoms, and severe depression from 8 out of 10 symptoms. Finally, in ICD-10, the diagnostic algorithm differs by requiring the presence of at least 2 out of the following 3 symptoms: depressed mood, loss of interest, and decreased energy for mild and moderate depressive episodes, and all 3 for severe depressive episodes. ICD-10 episodes with psychotic features exclude first-rank symptoms and bizarre delusions. In terms of core or nuclear symptoms, both DSM-IV and ICD-10 include the following symptoms: (i) psychic (eg, mood or anxiety or suicidal ideation and guilt feelings); (ii) psychomotor (eg, retardation or agitation); (iii) somatic/neurovegetative (eg, sweating, tachycardia, dryness of mouth); (iv) diurnal variation; (v) insomnia/hypersomnia; (vi) loss of energy; and (vii) cognitive symptoms (eg, difficulty concentrating and loss of memory). All these components can be present in the same patient (this is more likely to happen in the most severe forms), but more often some aspects (besides depressed mood or loss of interest or pleasure) are predominant, particularly in the early phase, where some patients can be “paucisymptomatic,” with a more prominent psychic or somatic or cognitive expression. However, along with the development of a full-blown major depressive syndrome, all core or nuclear symptoms tend to occur. Thus, depression is like the rings that a pebble makes in a pond, which enlarge progressively from the center (depressed mood and loss of interest), to progressively include more and more symptoms (psychic, somatic, and cognitive). In other words, depression evolves from an initial “paucisymptomatic” presentation to the full-blown, multisymptomatic form usually seen by the GP. Psychiatrists usually see patients at a later stage, after weeks of suffering, if they are not adequately diagnosed and treated by GPs. It is of paramount importance that GPs be aware that patients with a monosymptomatic presentation (depressed mood/anxiety and reduced interest or anhedonia), even though the 2-week criterion is not fulfilled or other symptoms are not present, may present subclinical signs that can quickly develop into the core or nuclear symptoms of a major depressive episode. The final point we must address is whether an antidepressant should be active on the core symptoms of depression. We favor a “holistic” approach to the psychobiology of depression taking into account dysfunctions of the serotonergic (5-HT) or noradrenergic (NA) pathways, as well as the fine regulation of disturbed biological rhythms involved in the pathogenesis of depression (such as the hypothalamic-pituitary-adrenal [HPA], melatonin, etc), which are responsible for diurnal variations in mood, sleep disorders, anxiety, neurovegetative symptoms, etc. Future approaches should address not only the classic monoaminergic pathways, but also other neurotransmitters and/or neuromodulators involved in the dysregulation of biological rhythms, which influence, at least in part, the pathophysiology and outcome of major depression.

REFERENCES

What are the core symptoms of depression?
What are the core symptoms of depression?

The concept of “depression” embraces a wide range of states of pathologically changed affects (from typical melancholic forms to atypical, masked, and seasonal, depressions). The core symptoms of depression determine the pathological course and the type of response to therapy, and form the basis of the psychopathological structure of depression. These manifestations of depression are also the main measures of compliance used to evaluate the action of psychotropic drugs (target symptoms). The basic symptoms of typical depression include positive affectivity manifestations (mentally oppressive depressive hyperesthesia (eg, heartache, suffering) or somatic disorders, which determine the clinical presentation of typical (vital) depressions. These core diagnostic features include: (i) melancholy, ie, an uncertain (protopathic) feeling of intolerable pressure in the chest or epigastrium (precardiac or epigastric melancholy) accompanied by low spirits, despondency, despair, hopelessness; (ii) intellectual and motor retardation, ie, difficulties in concentration and attention, delayed responses, slowness of movements, loss of spontaneous activity; (iii) pathological circadian rhythm, ie, mood swings during the day with maximum symptom severity early in the morning; (iv) ideas of self-inferiority, ie, persisting thoughts of self-uselessness and self-accusation, depreciation of personal successes in the past, pessimistic thoughts about the future; and (v) suicidal thoughts, ie, psychologically not derivable wish to die, thoughts that life is not worth living, suicidal ideation, occasionally an irresistible urge to commit suicide.

The diagnosis of atypical depressions is based on negative affectivity manifestations, involving mental alienation (persisting feeling of impoverished and altered mental life, loss of motivation to any activity). The symptom complexes of negative affectivity include: (i) anaesthesia psychica dolorosa, ie, a painful feeling of loss of emotions, inability to feel love, hatred, empathy, anger; (ii) depressive devitalization, ie, loss of life instinct, instinct of self-preservation, vital inclinations (sleep, appetite, libido); (iii) apathy, ie, appetency deficiency accompanied by a loss of zest for life, lack of energy, indifference to everything; (iv) dysphoria, gloominess, “anger attacks,” querulousness; and (v) anhedonia, ie, inability to experience pleasure, joy, and delight. The difficulty of detecting masked depressions (or “latent,” “alexithymic”), which are prevalent in general medical practice, is related to the predominance of neurotic symptom complexes (anxiety, phobic, hypochondriac, neurasthenic, autonomic and somatoform disorders, algias, sleep disturbances, mainly in the form of insomnia/hypersomnia), while the basic affect manifestations (melancholy, psychomotor disturbances, ideas of guilt) are moderate. In these cases, the diagnosis of depression is made easier by evidence of a circadian rhythm, pessimistic thoughts about the persons’ own health and future, passive suicidal thoughts (desirability of an accident, sudden death, etc). The diagnostic criteria for seasonal depressions are based on chronobiological characteristics, as these types of affective disorders manifest during the autumn and winter period. During spring and summer, depressions can be followed by a remission or hypomania. The peculiarities of the psychopathological structure of seasonal depressions should be taken into account. Two types of somatovegetative symptom complex can be distinguished in seasonal depressions: hyperesthetic (increase in appetite, including appetency for carbohydrate-rich meals, increase in weight, hypersomnia) and anesthetic (reduction in appetite and taste, accompanied by a nutrition deficit and considerable loss of weight, insomnia with absence of feeling of sleep and reduction of sleep duration).

The choice of antidepressants is based on the psychopathological manifestations of depressions as described above. Effective control of typical depression with basic symptomatology is achieved with the majority of current thymoanaleptics. Severe depression with agitation or marked psychomotor retardation requires use of potent psychotropic medications: injectable tricyclic antidepressants are preferable. In mild or moderate depressions, as well as atypical depressions, with predominance of negative affectivity, the recent antidepressants are the drugs of choice. Compared with tricyclic antidepressants these are much more neurochemically selective and produce fewer side effects (selective stimulators and inhibitors of serotonin reuptake, fluoxetine, paroxetine, etc; dual action antidepressants, including venlafaxine, mirtazapine, etc; selective, reversible monoamine oxidase A-type inhibitors like pirlindole, or other antidepressants like tianeptine). Finally, the acute treatment and prevention of seasonal affective disorder, which is associated with dysfunction of the serotonergic system and pineal gland, as well as of other depressions characterized by abnormal biological rhythms, relies on new therapeutic strategies interacting with circadian rhythms and other targets.
What is the epidemiologic and historical background to a modern definition of depression?

Given its huge epidemiologic variation, with point prevalences of Major Depressive Episode in the general population over 1 year ranging from 0.6% in Taiwan through 5% in France to 10% in the United States, it is essential to define the core symptoms of depression if we are to identify a nucleus of depression for use as a model in clinical psychiatric research and operating criteria for appropriate antidepressant treatment. The definition of depression is grounded in Eysenck’s description of melancholia as a state of “intense depression experienced with psychic pain and characterized by psychomotor inhibition.” The concepts of neurasthenia, neurotic depression, and anxiety and depression were then coined to characterize syndromes falling outside this definition. Since these comprised symptoms such as insomnia, functional somatic complaints and anxiety, clinicians were led to differentiate between “endogenous” and “psychogenic” depression—only for this distinction to be swept aside after 1960 by the arrival of the first antidepressants that proved active against all forms of depression, irrespective of their cause. International classification systems subsequently jettisoned the concept of endogenicity so dear to Kraepelin.

Core symptoms of depression

However, a number of psychiatric manuals differentiate between endogenous depression (whether unipolar or manic-depressive bipolar) and a much more mixed presentation extending from reactive depression to neurotic depression. Clinical studies have identified the following core symptoms across a multiplicity of presentations:

- Depressed mood (expressed in its most severe form as convictions of unworthiness, incurability, and guilt).
- Inhibition or loss of élan vital (asthenia, global disinterest, loss of initiative, impaired intellectual performance and motor function).
- Somatic symptoms (anorexia, weight loss, constipation, sleep disturbance).
- Anxiety and personality disturbances (irritability, impulsiveness, social withdrawal).
- Ideas of death and suicidal thoughts (often associated with depressed mood).
- Delusional ideas (in the most severe forms of depression): mood-congruent (guilt, ruin, mourning, misfortune, hypochondria) or mood-incongruent (ideas of influence and possession).

The introduction of international criteria advanced the understanding of depression by assembling experts who reanalyzed the literature data and drew on new studies. It was thus no surprise when, in 1994, the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) required at least either depressed mood or loss of interest to meet the criteria for Major Depressive Episode. Cognitive symptoms (diminished ability to think, concentrate, or take decisions) were also given a major role. It was specified that depressive symptoms vary with the branch of medicine concerned (in general medicine patients with depressive disorder report more pain and somatic illness than others) and age (predictions for irritability and social withdrawal in children, impulsiveness and toxic substance use in adolescents, and cognitive impairment in the elderly).

Disruption of circadian rhythm as a major symptom of depression appears only in the form of sleep disturbance (maintenance insomnia, early morning awakening insomnia, or, conversely, hypersomnia).

Response to antidepressants and clinical profile

Antidepressant response profiles appear to differ with the clinical characteristics of the depression: monoamine oxidase inhibitors in atypical depression (mood reactivity, increased appetite or body weight, hypersomnia, impression of limb anesthesia, oversensitivity to rejection); tricyclics and electroconvulsive therapy in melancholic depression; selective serotonin reuptake inhibitors in nonmelancholic depression. Depression with anxiety and sleep disturbance appears sensitive to the more sedative antidepressants.

Neuroimaging and understanding of the pathophysiology of depressive symptoms

The key to future breakthroughs could lie in the ability to identify specific symptoms with certain neuronal circuits and develop substances to target those circuits. The demonstration of structures mediating the self-referential processing of emotional stimuli and of corticostriatal circuits involved in depression justifies further research into the connections between clinical symptoms and functional neurology. Depressive symptoms may thus be divided into spheres:

- Emotion: depressed mood, self-deprecation, guilt.
- Motivation: loss of interest, loss of affect, psychomotor retardation.
- Association: abnormal executor function, with each sphere being concerned by a neighboring, but different, neuronal circuit. A pathophysiological approach to depression brings the clinical targets of antidepressants into sharper focus. Depression is a clinically mixed syndrome with core characteristics that are recognized by all clinicians. The next step is to establish cliniconeurophysiologic correlates that optimize the deployment of our therapeutic arsenal.
What are the core symptoms of depression?

There are two possible presentations of depression:

1. Presence of one symptom (or a group of symptoms) pathognomic for depression, which leads to an immediate diagnosis of depression; or
2. Absence of characteristic symptoms, in which case it is the ensemble of a more or less variable clinical picture that leads to diagnosis of the disorder. The first presentation is the classic one in psychiatry. Since Kurt Schneider, 1 “vital sadness” has been considered as a fundamental symptom of depression. Depressed mood is described as having a “different quality” than “normal sadness.” It is sadness that is nonreactive, internal, “corporalized,” persistent, not voluntarily changeable. For these authors, this symptom is the very core of depression, it is depression itself. This type of depression is described as endogenous, 2,3 and is characterized by inhibition, lack of emotional reactivity, and loss of interest and pleasure in things. The second presentation is increasingly at the forefront in current practice. Modern operating classifications have switched from the former endogenous (melancholy)/reactive (neurotic) distinction to that between major depression and dysthymia. They postulate a sequential development of the different subtypes of depression throughout the subject’s evolution. These classifications do not take into account the subtle phenomenological distinction of the “different quality” of the depressive mood, which is so difficult to detect. 4 It has been claimed that this devaluates the symptom, and blurs the limits between the syndrome and the pathological entity and the different types of mood disorder. However, the basic diagnostic criteria continue to include an alteration of mood and a lack of pleasure, with various combinations of the following symptomatic complexes later completing the picture:

1. Psychic: sadness, demoralization, lack of interest, negative thoughts, low self-esteem, decreased attention and memory, etc.
2. Somatic: anorexia, asthenia, weight loss, sleep disorders, pain, psychomotor retardation, etc.

From a practical perspective, the high incidence of depression has resulted in its being treated essentially at primary health care level. This patient population has a lesser prevalence of dysphoria or ideas of guilt, but a high incidence of fatigue, 5 which has been proposed as the primordial symptom of major depression. 6 We need to improve the early diagnosis and recognition of depression in this setting, for example, by using certain simple epidemiological screening tools and evaluation scales (Primary Care Evaluation of Mental Disorders [PRIME-MD], Mini-Mental Status Examination [MMSE], Zung Self-Rating Depression Scale [SDS], etc). 7,8 Physicians need to carry out appropriately detailed clinical interviews that cover the full psychopathological gamut of symptoms in order to improve the detection rates of depression. Another factor that adds to the difficulties is the lack of stability in symptoms throughout the course of the depression. This was clearly shown in a recent study, 9 with respect to both the continuity of symptoms in successive recurrences and the subtypes of depression. Variations based on gender have also been reported. 10 Likewise, transcultural divergences have been pointed out when studying samples in different populations. 11 However, all of these studies suffer from having been performed on samples of severe patients, frequently in hospital, which may not be very representative of the usual setting in which depression occurs. One field of interest over recent years is that of the importance of residual symptoms (fatigue, anxiety, sexual dysfunction, sleep disorders, etc), 12 which may persist after partial relief from symptoms following treatment of the episode. These residual symptoms multiply the risk of relapse by three, worsen social and occupational functioning, favor chronic depression, and increase the risk of suicide. Although it is debated whether these residual symptoms are caused by comorbidity with personality or anxiety disorders, they are...
now considered a prime target of antidepressant treatment, with the aim of achieving total remission and/or effective treatment of these symptoms. Further research is necessary, in particular through naturalistic studies, in order to gain a clearer picture of the clinical reality of depression. Reliable biological markers to validate clinical diagnoses are still lacking. Hopes have been placed on research into molecular genetics, neuroimaging, and neuropsychology, and new discoveries are expected, which should lead to a better understanding and delimitation of depression, as well as to benefits in the field of antidepressant treatment.

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Depression with accompanying biological, behavioral, and cognitive changes is the most common form of mental disorder in the community. A vigilant primary care physician, the “gatekeeper” of health care, is crucial in early detection, prompt and effective treatment, adequate rehabilitation, and prevention of depression. Proverbially, the term “depression” is equated with a feeling of sadness. Variability in clinical manifestations, natural course, comorbidity, associated disability, or impairment, and its impact on the considerable underrecognition of the disorder is well documented. Guidelines for diagnosis and detection of depression emphatically state that not all clinically depressed patients are sad and that many sad patients are not clinically depressed. Depression is not a normal reaction to life’s difficulties. Depression disorder consists of a group of symptoms and signs lasting 2 weeks or more. Presence of pervasive sadness or lack of interest in pleasurable activities or its equivalents is essential for the diagnosis of depression. Diagnosis is easier when the patient mentions feeling sad or depressed. Apathy, anxiety, irritability, and reduced interest or capacity for pleasure or enjoyment may be experienced in addition to or instead of sadness. Though affective symptoms are cardinal, cognitive, behavioral, and somatic symptoms are integral to the clinical presentation. Social stigma, or viewing depression as personal weakness, results in reluctance to seek or accept the diagnosis. Victims of the disorder strive to find a physical cause for their discomfort. Hence sleep disorders or vague somatic symptoms tend to be frequent presentations. Pain, particularly if the patient reports three simultaneous pain symptoms, indicates depressive disorder. Standardized classification systems like the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) specify that besides reduced interest or sadness, at least four additional symptoms drawn from a list that includes vegetative symptoms, psychomotor activity, cognitive symptoms, and suicidal ideation, are a diagnostic requirement. Children and adolescents tend to describe their mood as irritable rather than sad. In addition to the context of primary mood disorders, symptoms of depression can occur in the context of obsessive, panic, eating, and generalized anxiety disorders, as well as drug and alcohol abuse. Symptoms and typical syndromes of depression are frequent in nonpsychiatric disorders such as grief reaction, substance abuse, intoxication, or withdrawal, and in purely physical disorders like diabetes, cancer, heart attack, stroke, and after use of prescription drugs for some of these disorders. The treating physician should thus determine whether there is a relationship between the symptoms of the primary physical illness, the effects of the administered drugs, and affective symptoms. The sequence of occurrence of symptoms, and the nature, intensity, diurnal fluctuations, past and family history of depression, help to diagnose...
Instruments like the Depression Screening Questionnaires facilitate the diagnosis of depression. Ultimately, the combination of clinical awareness, vigilance, and diagnostic orientation of the primary care physician is critical to early recognition of a depressive disorder. Once the presence of a depressive disorder is diagnosed, a finer analysis is required to subtype the disorder. Age, education, race, income, and marital status are related to the outcome more than the presentation. Psychosocial events may influence the first few episodes, but do not have much relevance in subsequent episodes. An ideal antidepressant drug is definitely on any clinician’s wish list. The ten tenets for an ideal antidepressant drug should be:

✦ Rapid onset, broad spectrum of action in all subtypes of depression.
✦ Achieve complete remission, promote functional recovery, prevent relapse.
✦ Safe in overdose, pregnancy, lactation, and in cardiac, respiratory, autoimmune, skin, hepatic, renal, and other systemic disorders.
✦ Minimal drug interactions.
✦ Established safety for long-term use in all age groups.
✦ Absent or minimal adverse and emergent effects on weight, hair growth, appetite, libido, and others.
✦ No diurnal sedation.
✦ Easy to administer, preferably once daily standard dose, no dose titration.
✦ Cost-effective, easily available.
✦ Low risk of breakthrough mania.

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UNMET NEEDS IN DEPRESSION (AND OTHER MENTAL DISORDERS)

Interview with N. Sartorius
Switzerland

Mental health needs should no longer be expressed in terms of prevalence of mental disorders as such, but in terms of demands for which an adequate response is available to mental health services. Therefore, assessment of needs should take into account not only what the patient wants, but also the needs of families, doctors, and society. The main difficulty in the application of this definition is that the needs and demands of each party may be conflicting or show only partial overlap. What patients want, for example, is to be treated with dignity, to be free of symptoms, and to retain their source of income (jobs). Family needs include the preservation of their reputation and financial situation. Doctors want to be effective, avoid litigation, be confident that the risk of suicide is low, and that treatment will have a rapid onset of action and not be unduly long. Governments (voicing society’s demands) want to reduce the cost of care, while remaining in tune with their election platform.

They, however, request a service, get it, and feel better. It is therefore more useful not to equate prevalence data with needs — were that done, there would also be the danger that every change of diagnostic criteria would change the assessment of needs — but to define mental health needs as demands for care made by people who have a mental disorder for which the health services have an effective response acceptable to the persons demanding help and to the society in which they live. To the estimate of needs defined in this way, it is necessary to add work that should be done to look after persons whose mental disorder is of such severity that insight into their state is significantly impaired and who require medical help necessary to prevent them from harming themselves or those around them. These cases, however, represent only a relatively small proportion of the total numbers of people who are using mental health services.

Are there any problems that make the assessment of needs defined in this way difficult?

The main difficulty does not lie in the assessment of needs and demands, but in the fact that the needs and demands of the various stakeholders in mental health care are not the same (see Figure).

What patients want overlaps only partially with what families and society want. Patients, for example, may demand the best of care regardless of its cost. Families may be keen on preserving their prestige and avoiding embarrassment from the unusual behavior sometimes seen in mental illness (regardless of the type of treatment) and would not object to hospitalization far from home or other ways of hiding the patient. Governments...
may want to reduce costs for care by focusing on certain groups of disorders and providing the least expensive service. All three would like to see the illness disappear, but in its presence will demand or do different things to resolve the problems.

Can you give us another example illustrating the relevance of this approach to the assessment of needs?

Another example is the often quoted desideratum that treatment must be simple. The argument is that this will allow less well-trained personnel to apply the treatment and that compliance with the instructions of the service provider to the patient will be better. The requirement that treatment be simple stems from priorities of the health service, which aims to simplify training and to delegate treatment responsibility to less expensive staff. Patients do not express that need. In fact, both the experience of traditional practitioners and of medical practice seem to indicate that patients are prepared to follow very complex treatment regimens provided that they have received instructions about the treatment and that they believe that, if taken in the specified way, the treatment will help.

Another common example is the family’s demand to the health worker to find a treatment that will make the patient’s sleep/wake rhythm predictable and coinciding with theirs. While a patient may not feel the need to take sleeping pills and might even prefer being awake for a great part of the night, the family finds this difficult to tolerate because of their obligations during the day. Recognizing the difference between what patients and families need and taking it into account will require that doctors use their negotiating skills with both parties in order to find a compromise solution. If they do not, they will lose the good will and confidence of one or both of the crucial parties involved in the treatment process—the patients and/or their families.

Tell us more about the needs that patients express?

Research on expressed needs and demands has only recently begun to take on more serious dimensions. Until now, such studies were not seen as a priority and it was difficult to find funding for them. What we do know is that patients wish to be treated with due respect to their dignity; that they want to be involved in decisions about their treatment; that they demand easy access—whenever necessary—to the service providers; that they wish to be freed from symptoms that are severely disturbing (some symptoms of mental disorders are not experienced as too much of a nuisance by the patient); that their disease—if it cannot be eliminated—does not affect functions that they consider most important (for example, their thinking or their sexual functioning); that they do not remain for ever marked by the disease; and that their sources of income—eg, their job—is not affected by the illness.

These examples of patients’ wishes and expectations were found in a major project against stigma started a decade ago and currently under way in some 18 countries. These findings may not be valid everywhere, and it is therefore extremely useful to carry out local studies to find out what the patients’ needs are.

What about families’ needs?

Here, even more than with patients’ needs, it is important to carry out assessments in the cultural setting in which the service is provided because the needs of families tend to be profoundly affected by traditions and other cultural markers of a community. In many countries, families are reported to go to extreme lengths to protect their good reputation; they try to avoid financial crises because of one of its members’ sickness; they will often have only a limited amount of patience in waiting for their sick member to reassume his/her role in the family; and they will insist on having a decisive word in decisions about the patient’s treatment. They will also often refuse to take on—forever—the burden that a sick member imposes; for the family as well as for the patient it is incomparably easier to fight if the end of the disease is in sight, even if very distant.

And what about the doctors’ needs?

Doctors want to help their patients, but also want to avoid litigation; they want to be reassured that the risk of suicide in a patient they have to treat is low; they want to see a rapid onset of treatment—not only because they want to help the patient, but also because they want to see the good results of their work; they want to learn about techniques that can shorten the duration of their intervention; and they want to be able to refer away patients whose treatment is beyond their competence.

And society’s needs?

In democratic societies, governments are “spokespersons” for society as a whole (or at least 51% of it). Governments, however, rarely have the luxury of fulfilling long-range plans and usually have to change them for political reasons. This also changes governments’ demands on the health sector. Still, it seems that some demands are becoming universal. Governments want health services to help them contain disruptions of communities that they fear might arise if patients with mental illnesses were to be allowed to go about unattended; they want to reduce the cost of care and keep it low in all sectors with the exception of those that are politically very important and therefore often very visible; they want to build and retain their image in harmony with their election platform, which often contains the solution of some, but certainly not all, health problems; and they want to avoid scandals which involve them.

What about unmet needs concerning treatment?

Today’s array of medications and techniques that have been shown to be effective and safe is considerable, certainly larger than ever before. The main challenge therefore does not lie in the development of better treatments, but in the equitable use of those available. Stigma of mental illness reduces the priority given to the development of effective mental health services. Burnout of personnel in institutions dealing with mental illness is on the increase, fueled by an excessive amount of work (with continuous reduction of personnel and other resources) and unrealistic expectations. Ignorance about mental illness and ways of dealing with people who have it is monumental. Also, the disintegration of families and communities reduces their capacity to deal with their ill members. These are challenges that have to be addressed if the currently available treatment techniques are to give maximum benefit and satisfy the mental health service needs of the population.

Does this mean that we do not need to improve treatment techniques?

No, improvement of therapy is very useful, but it will not be sufficient. Advances must go hand in hand with an adjustment of the health system and an active commitment of society to deal with mental disorders in the best way known.
**Besoins insatisfaits dans la dépression (et autres troubles mentaux)**

Les besoins dans le domaine des maladies mentales ne devraient plus être exprimés en termes de prévalence des troubles mentaux en tant que tels, mais en termes de demandes pour lesquelles il existe une réponse adéquate sur le plan des services de santé mentale. L'évaluation des besoins doit prendre en compte non seulement les souhaits du patient, mais également ceux exprimés par les familles, les médecins et la société. La difficulté principale liée à l'application de cette définition est que les besoins et les demandes de chaque partie peuvent être en conflit ou ne se recouvrir que de façon partielle. Ce que demandent les patients, par exemple, c'est d'être traités avec dignité, d'être soulagés de leurs symptômes, et d'être sûrs que leurs sources de revenus (emplois) ne soient pas affectées par leur maladie. L'évaluation des besoins des familles comprennent entre autres
THE IMPACT OF SLEEP DISORDERS ON THE COURSE OF DEPRESSION

by R. Emsley, South Africa

This article looks at the pivotal importance of sleep-associated sleep abnormalities throughout their course: from diagnosis at the early stage of depression to initial treatment, and to their long-term outcome.

The quality of life of depressed patients is diminished by a variety of factors, sleep disturbances being one of the most prominent among these. Very few patients with depression do not experience disturbance of sleep pattern in one form of another. Sleep disturbances in depression comprise insomnia and, less commonly, hypersomnia. Some patients actually fluctuate between these two patterns of sleep disturbance during the course of an episode of depression, reflecting the psychobiological heterogeneity of major depressive episodes. Whether as insomnia or hypersomnia, it has become clear that sleep dysregulation is more than just an epiphenomenon of depression. Thus, not only is disturbed sleep one of the most common concomitants of a persistent depressed mood—additional associations include the following: (i) the presence of sleep abnormality in depressed patients has prognostic and outcome implications; (ii) the majority of antidepressants cause substantial changes in subjective aspects of sleep; insomnia; depression; major depression; antidepressants and the conventional monoamine oxidase inhibitors

sleep physiological processes may be intimately involved in the pathophysiological and recovery processes of major depression. Insomnia associated with depression can be categorized as follows: difficulty initiating sleep; difficulty maintaining sleep (or continuity disturbances); and early morning awakening. Difficulty initiating sleep is the least specific; and early morning awakening the most specific to major depression. Factors such as age, sex, severity of the episode, and comorbid anxiety play a role in determining the incidence, severity, and nature of sleep disturbances associated with major depression.

Time course

Sleep abnormalities in depression are seen across the age spectrum, from an early age, ie, in adolescence, to the elderly. The bidirectional risk rela-

Almost all patients with major depression experience a disturbance of sleep pattern. Sleep disturbance is a core feature of major depression, and is associated with important prognostic and outcome implications. While sleep abnormalities with major depression are seen across the age spectrum, aging is associated with more prominent insomnia. Disordered sleep precedes the onset of a depressive episode, and the reemergence of insomnia may herald the onset of a new episode of recurrent depression. While insomnia often resolves with successful treatment of the depressive episode, most polysomnographic sleep abnormalities persist after recovery, suggesting that they are more trait-like than state-like. Excessive daytime sleepiness and fatigue are consequences of insomnia, and can result in decreased productivity and an increased risk of accidents. Persistent sleep disturbance is associated with significant risk of recurrence, an increased risk of suicide, and poorer overall outcome. Most antidepressants cause substantial changes in subjective aspects of sleep as well as in polysomnographic measures. Tricyclic antidepressants and the conventional monoamine oxidase inhibitors

suppress rapid eye movement (REM) sleep to varying degrees. Selective serotonin reuptake inhibitors (SSRIs) generally suppress REM sleep, but are often associated with subjective reports of insomnia. Insomnia in patients with major depression requires careful assessment. Exclusion of primary insomnia, as well as of general medical and substance-related causes, is important. Treatment strategies involve pharmacological and nonpharmacological interventions. Some clinicians prescribe an antidepressant with sedative properties. Alternatively, a hypnotic can be coprescribed. Neither of these approaches is without problems. Sleep hygiene and other behavioral treatments may be helpful adjuncts.

Keywords: sleep; insomnia; depression; major depression; antidepressant

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tionship between sleep and depression may be particularly strong in older adults. Aging is associated with more prominent insomnia in depression, while hypersomnolence is relatively more common earlier in life and may even be nearly as prevalent as insomnia among younger depressed women. There is considerable evidence to suggest that disordered sleep actually precedes the onset of a depressive episode. In a longitudinal epidemiological study investigating the association between sleep disturbance and psychiatric disorders in young adults, prior insomnia was a significant predictor of subsequent major depression. On the basis of their findings, the authors suggested that complaints of 2 weeks or more of insomnia nearly every night might be a useful marker of subsequent onset of a major depressive episode. In the National Institute of Mental Health Epidemiologic Catchment Area study, 10.2% and 3.2% of a community sample noted insomnia and hypersomnia, respectively. The risk of developing new major depression was significantly higher in those who had insomnia compared with those without insomnia, but this risk was much reduced if the insomnia had resolved at a follow-up visit. In subjects with preexisting major depression the reemergence of insomnia can similarly herald the onset of a new episode of recurrent depression.

Considerable research attention has focused on whether sleep changes occurring in major depression are state-related (ie, emerge during the episode only) or trait-related (ie, whether they persist after full remission of the episode). Research to date has produced mixed results. On the one hand, improvement in subjective insomnia was found to be closely related to global improvement in depression, and it was originally thought to be a state marker. This is also supported by findings that hypothalamic-pituitary-adrenal (HPA) axis changes appear to be specifically state-related. On the other hand, longitudinal studies in fact indicate that most EEG sleep measures persist after episode recovery, suggesting that they are more trait-like. There are indications that the type of treatment may have an effect on sleep in the postrecovery phase of depression. A study reported quantitative differences in EEG sleep measures in subjects who had recovered from a major depressive episode after treatment with interpersonal therapy and those who recovered after treatment with interpersonal therapy plus fluoxetine.

**Classification**

Sleep EEG changes, together with HPA axis changes associated with major depressive disorder are among the best replicated biological findings in psychiatry. Sleep disturbances in patients with major depressive disorders can be classified according to polysomnographic studies as: (i) difficulties initiating and maintaining sleep; (ii) abnormal sleep architecture; and (iii) disruptions in the timing of rapid eye movement (REM) sleep:

- Difficulties with sleep initiation and maintenance include prolonged sleep latency (ie, sleep-onset insomnia), intermittent wakefulness and sleep fragmentation during the night, early morning wakening with an inability to return to sleep, reduced sleep efficiency, and decreased total sleep time.
- Regarding abnormal sleep architecture, abnormalities have been reported in the amounts and distribution of non-rapid eye movement (N-REM) sleep stages throughout the night, including an increase in the amount of light stage 1 sleep and reduction of deep, slow-wave (stages 3 and 4) sleep.
- REM sleep disturbances in patients include a shortening of REM latency (<65 minutes), a prolongation of the first REM sleep period, and increased REM density (ie, increased total REM sleep time), particularly in the first half of the night.
- Sleep disturbances can be verified with polysomnography in 90% of patients with major depression. They are most pronounced in melancholic depression and in bipolar and psychotic depression.

The underlying mechanisms involved in the pathogenesis of sleep abnormalities in major depression are not known. In cases of early morning wakening and decreased REM latency there may be a phase advance of the sleep-wake cycle. Although not fully elucidated, a recent study involving EEG sleep and regional metabolism assessments with positron emission tomography reported interesting findings regarding the underlying neurobiology of disturbed REM sleep in depression. Depressed patients showed signs of altered function of limbic/anterior paralimbic, and prefrontal circuits during the REM sleep state, possibly reflecting an imbalance in monoaminergic/cholinergic function affecting not only the brainstem generation of REM sleep, but also the manner in which the forebrain responds to the stimuli of REM sleep.

Sleep disturbances seem to be more prominent in patients with more severe depression, as suggested by the finding that they were reported in 80% in patients with depression (presumably more severe) compared with only 40% to 60% depressed outpatients. About 30% depressed patients actually have hypersomnia. When EEG sleep profiles were compared in the first 6 weeks of a depressive episode in a group of subjects with recurrent depression and compared with their sleep profiles as measured during their previous episode at a later stage, it was found that REM sleep abnormalities were more pronounced earlier in the course of a depressive episode. Deficiencies in sleep efficiency may explain why depressed patients often feel fatigued even when they appear to sleep excessively. However, the diagnostic specificity of the sleep disturbances is poor. It has been reported that no single sleep variable reliably distinguishes patients with major depression from healthy controls or from patients with other psychiatric disorders.

**Clinical implications**

Excessive daytime sleepiness and fatigue are unavoidable consequences of insomnia, and are therefore common features of patients suffering from depression. This in turn can result in impaired occupational and social functioning, with decreased productivity and an increased risk of accidents.
There are other important clinical implications for sleep disturbances in depression. Persistent sleep disturbance is associated with significant risk of recurrence. Also, recurrent depression is associated with a more severe neurophysiologic substrate than phenotypically similar single-episode cases. Two studies have reported an association between sleep disturbance and suicide. The first found that both insomnia and hypersomnia are associated with suicidal behavior in patients with major depression, and the second reported an association between poor subjective sleep quality and suicidal behavior in patients with major depressive disorder. Polysonomographic sleep changes such as REM latency have also been reported to predict treatment response and the clinical course of illness.

**Effects of antidepressants on sleep**

All antidepressants have some effects on sleep architecture. In fact, in early studies, suppression of REM sleep was regarded as necessary for the antidepressant action, based on a finding of a correlation between clinical response and REM suppression as well as a temporal relationship between the onset of clinical response and REM suppression. However, this was later found not to be the case.

Clinical trials investigating the effects of antidepressants in patients with major depressive disorder have reported varying effects of these agents on sleep latency and sleep efficiency, as well as on daytime somnolence. Some antidepressants have profound effects on sleep regulation, and others minimal. Specific antidepressants also vary in their effects from individual to individual. An antidepressant may produce a strong sedative effect in one individual, and no effect or even an activating effect in another. Clinicians have traditionally selected an antidepressant with a more sedative profile for depressed subjects with prominent insomnia, while a more activating antidepressant may be prescribed in cases where hypersomnia is a significant problem. It has also been suggested that the nature of the sleep disturbance at initial clinical presentation may be relevant to the choice of antidepressant medications and the likelihood of experiencing treatment-emergent side effects.

**Tricyclics**

The tricyclic antidepressants (TCAs) primarily inhibit the reuptake of the neurotransmitter norepinephrine, and to a lesser extent serotonin. They have additional effects on a variety of other receptors. Most of the TCAs are potent suppressors of REM sleep, although some do so only moderately. Clomipramine and desipramine are the most potent in this regard. REM suppression is usually more pronounced during the first few hours of sleep and there is some accommodation to these effects with continuation therapy. TCAs also prolong REM latency and decrease the total amount of REM sleep time. Clomipramine, desipramine, and amitriptyline increase stage 1 sleep and decrease sleep efficiency over baseline levels. Clomipramine, with the strongest serotonergic effects of all of the TCAs, has the most prominent alerting effect on sleep. The clinical response to amitriptyline and clomipramine may be related to the degree of REM sleep suppression, with better outcome being associated with a greater degree of REM suppression. One curious TCA is trimipramine. Although a classic TCA, trimipramine shows unusual pharmacologic properties. Rather than reducing, it increases, REM sleep. This property has important clinical implications. Clinicians have for many years found trimipramine particularly useful in depressed patients with prominent insomnia, and in addition it has been shown to be effective in treating non-depressed patients with primary insomnia.

**Monoamine oxidase inhibitors**

Monoamine oxidase inhibitors (MAOIs) have been found to also suppress REM sleep in patients with major depression. The onset of the suppressant effect is delayed, however, and there is considerable associated REM rebound upon withdrawal. Unlike in the case of TCAs, the antidepressant response to phenelzine treatment is not correlated with the degree of suppression of REM sleep. MAOIs also reduce total sleep time and may decrease sleep efficiency. Different findings to the classic MAOIs have been reported with the reversible MAOI moclobemide. One study reported improved sleep continuity in depressed subjects, particularly during the intermediate and late stages of drug administration in a 4-week trial. This was accompanied by significant improvements in the symptoms of depression. A second study found an activating effect with moclobemide, most marked during the early phase of treatment. The most noticeable effects were on REM sleep, affecting polysomnographic and spectral sleep EEG parameters. A REM sleep habituation phenomenon was observed, and a slight REM sleep rebound effect occurred early during withdrawal.

**Selective serotonin reuptake inhibitors**

Serotonergic neurons play a critical role in modulating the onset and maintenance of sleep, and it is thought that insomnia in depression is linked to dysfunction of central nervous system serotonergic systems. Selective serotonin reuptake inhibitors (SSRIs) generally suppress REM sleep. However, they have variable effects on subjective reports of effects on sleep. Between 10% and 15% of patients treated with an SSRI complain of insomnia during the early stages of treatment. As a consequence, clinicians often coprescribe concomitant hypnotic medication. One source found that 35% patients prescribed an SSRI also received a sedative/hypnotic. Studies have highlighted increased wakefulness with SSRIs, particularly on fluoxetine. A study investigating the longer-term effects of fluoxetine in patients with major depression who were treatment responders reported significantly reduced sleep efficiency, decreased stage 2 sleep, increased stage 1 sleep, prolonged REM latency, and a 3.4% reduction in REM time at 10 weeks of treatment. This study showed that these effects persist, as even after 30 weeks of treatment there were still alerting effects on sleep. Paroxetine is also associated with an
alerting effect as well as a significant REM rebound with discontinuation. Fluvoxamine also appears to have an alerting effect in patients with major depression. This effect was found to have a fast onset, being evident even after the first day or two of treatment. Citalopram did not appear to have any deleterious effects on sleep continuity or wakefulness during the night in a study of patients over 6 weeks of treatment. Escitalopram is reported to cause insomnia at a greater rate than placebo.

Other antidepressants

Mirtazapine is a potent blocker of 5-HT₂, 5-HT₃ and histamine receptors, and it has the strongest initial sedative effects among the newer antidepressants. These effects cause daytime sedation in about half of patients during the first 2 weeks of treatment, but they may be very useful for depressed patients with prominent insomnia. In a study employing low doses of venlafaxine, the effects on sleep architecture were similar to those of the SSRIs. Bupropion is generally considered to be an activating antidepressant, and has been reported to shorten REM latency and increase REM sleep. Reboxetine, a selective norepinephrine reuptake inhibitor, has been reported to induce sleep-EEG changes similar to those after SSRIs by increasing intermittent wakefulness and decreasing REM time.

Treatment options for insomnia associated with depression

Insomnia is a symptom with many possible underlying causes. Careful assessment and establishment of a differential diagnosis is necessary. It is important to rule out a primary sleep disorder as the cause of the insomnia as one of the first steps. A significant association has been reported between primary sleep disorder and major depression. There is an increased risk of depression in patients with restless legs syndrome as well as sleep apnea, and effective treatment of sleep apnea appears to improve depression in these patients. A further important reason for ruling out primary sleep disorders is because some of the medications used to treat insomnia associated with depression can actually exacerbate the primary sleep disorders. Once identified, primary sleep disorders should be referred to a sleep specialist. There are numerous other possible causes of insomnia. Insomnia may also be related to a general medical condition, whether due to pain, discomfort, or a more direct physiological mechanism. Examples of the latter include hyperthyroidism and pheochromocytoma. Insomnia may be related to a side effect of medication, or to the use of some other substance. Both substance (eg, alcohol) intoxication and withdrawal may cause insomnia. In attempting to improve sleep patterns, patients with insomnia may sometimes use medications inappropriately. This may include the use of hypnotics or alcohol to help them sleep at night, as well as caffeine or other stimulants to combat excessive daytime fatigue. Alcohol dependence is often associated with prominent, persistent insomnia. Insomnia may also be related to a psychiatric disorder other than depression (eg, anxiety disorder, mania, psychosis). There are various strategies for treating patients with insomnia in major depression. First, an antidepressant with sedative properties can be prescribed. Mirtazapine is commonly used these days, although sedative TCAs such as amitriptyline and trimipramine, trazodone, and nefazodone have also been used. Patients successfully treated with an SSRI, but who experience persistent insomnia, may be treated with a hypnotic such as zolpidem or zopiclone. Alternatively, they may be switched to a sedating antidepressant. Finally, combinations of antidepressants (ie, adding a sedative antidepressant at night to a patient being treated with an SSRI) can be considered as a last resort in patients responding inadequately to the above strategies. However, caution is necessary with the TCAs because of potentially toxic effects due to drug-drug interactions, and combination of an SSRI with mirtazapine is likely to be safer.

In addition to pharmacologic management, sleep hygiene and other behavioral strategies can be helpful in treating insomnia associated with major depression. Activities that may be detrimental to optimal nighttime sleep should be eliminated. These include things such as daytime napping, excessive alcohol consumption and brisk exercise in the evening, and excessive daytime caffeine intake. Other behavioral treatments include stimulus control therapy (aimed at breaking the cycle of problems commonly associated with initiating sleep), sleep restriction therapy, relaxation and biofeedback therapy, and chronotherapy (resetting the biological clock by progressively phase-delaying sleep).

Conclusion

Since insomnia associated with major depression causes subjective distress and is associated with many risks, its optimal management must be an important clinical goal. Clinicians have for a long time been aware of the importance of the effects of antidepressants on sleep when choosing a drug to treat major depression. Previously, such decisions were based largely on clinical experience. Today, much research has been conducted, and we have a better understanding of the specific effects of individual antidepressants on sleep regulation. However, there is still a lack of consensus on the management of insomnia associated with major depression. Consequently, long-term treatment of insomnia is driven primarily by the individual choices of patients and their clinicians. Clinicians are frequently faced with a difficult choice when dealing with depressed patients with prominent insomnia. Prescribing an antidepressant with an activating effect may exacerbate the sleep disturbance, and coprescription of a hypnotic goes against the basic principle of avoiding polypharmacy where possible, as well as introducing the inherent risks of hypnotic therapy. Using a sedative antidepressant is therefore often regarded as a better option. However, this may result in a spillover of daytime sedation, and also complicate the return of normal sleep-cycle in recovering patients. □
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The impact of sleep disorders on the course of depression – Ensilver.
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Hygeia versus Polymnia*  
Some French painters and their diseases  
by C. Régnier, France

In the year 1700, Bernardino Ramazzini (1633-1714), doctor of medicine and philosophy, holder of the chair of practical medicine in Padua, published De Morbis Artificium Diatriba [Concerning Work-Related Diseases], the first “modern” work devoted to occupational illnesses. A second edition was published on the year of his death (with 12 additional chapters), and was translated into French in 1777. The author had ventured into several artists’ studios in the republic of Venice, and described many ailments induced by noxious substances, unhealthy working conditions, and the repetition of unusual movements.

Ramazzini noted a marked similarity between the clinical manifestations of painters and those of metal workers, “which differed only by their lesser intensity in painters.” Chapter 8 of his work was devoted to painters’ diseases such as “tremor, cachexia, black teeth, pallor, melancholy, and loss of sense of smell.” “Often, Ramazzini noted, when painting portraits, they endow their sitters with greater beauty and color

Painters are not an exception, they also suffer from diseases. Some occur due to chance or genetics, others are related to their artistic activity (professional diseases). The repeated use of organic solvents and pigments containing heavy metals or harmful substances have in the past caused a multitude of diseases due to intoxication (then not understood). The occurrence of disease in an artist inevitably upsets his or her perception of the world; this upset can prove critical in painters who express their impressions and feelings in their work. Psychiatric disturbance, loss of vision, neurological disorders, articular ailments, and painful syndromes can transform, modify, or even interrupt a painter’s oeuvre. Several French painters have been affected by diseases that gradually influenced their artistic work. For example: Édouard Manet (locomotor ataxia), Edgar Degas (loss of vision), Auguste Renoir (rheumatoid arthritis), Vincent van Gogh (character disorders), Henri de Toulouse-Lautrec (pyknodysostosis), and Raoul Dufy (rheumatoid arthritis). However, the different histories show that disease was never an obstacle to the expression of true artistic genius; in the best case, the painter adapted to his condition by finding new ways to express his art, or, in the worst case, died young while exploiting the time he had left by an explosion of creativity.

*(see French abstract on page 287)
than nature has in fact endowed them, as they themselves lack color and portliness.” Ramazzini also claimed that the sedentary life that painters led and “the fantastic ideas that perturb them resulted in a sort of melancholy genius.” He remarked on the “obnoxious smell of latrines that permeated artists studios (…) they continually breathe in these pernicious vapors that (…) disturb the management of the natural functions and lead to all the diseases we have noted.”

A Danish study of 1988 confirmed these observations: painters who used bright colors (rich in metallic pigments) were frequently affected with articular disease. There were also the “lead colics” (known since ancient Greece) and observed in the 16th century by Jean Fernel, personal physician to Henry II, who described a painter of Angers who had the habit of sucking his paintbrushes to clean them.

**Edouard Manet’s ergotism**

Manet died on April 30, 1883 at the age of 51 years. His left leg had been amputated several days previously because of gangrene.

In 1880, Manet’s doctor, François Siredey (specialist in women’s diseases), advised him to start hydrotherapy to treat clinical signs of incipient locomotor ataxia. Were these in fact manifestations of tertiary syphilis, which is characterized by disorders of coordination and equilibrium, paralysis, and proximal anesthesia of the lower limbs? Manet regularly attended shower sessions in the hydrotherapeutic establishment of Doctor Joseph Béni-Barde in Auteuil. “When the Bénibardeuses (thus he nicknamed the female attendants) see me running down the steps of the swimming pool and laughing, I will have won — and that could be quite soon,” he wrote to his friend Antonin Proust, who had been a school pal at Rollina College when they were ten. When Proust became minister of arts, in 1880, he awarded Manet the Legion of Honor.

In 1881, Manet was treated in Meudon at the Bellevue Clinic. These cures failed to provide the hoped-for benefits, so he switched to another doctor who prescribed rye smut (ergot), of which there then three forms: Bonjean’s Ergotin, Yvon’s Ergotin, and Tanret’s Ergotinin. The results were spectacular, and Manet decided to increase the dosage to what were horrifying levels according to his friend, the painter Camille Pissarro. The clinical signs of ergotism soon set in: hallucinations, delirium, circulatory disorders of the lower limbs, and the famous Saint Anthony’s fire that burned his legs.

From 1881, Manet regularly used a walking stick, and the following year he had great difficulty getting about. Doctor Siredey warned Antonin Proust that Manet should avoid such blatant overdosing. Holidaying in Meudon in the summer of 1882, Manet had become almost impotent. At the end of March 1883, his left foot had become gangrenous. Manet’s surgeon René Marjolin and doctors Siredey and de Berio, were in favor of amputation. On April 10, they called in Paul Tillot, a well-known surgeon at Beaujon Hospital, and Aristide Verneuil, professor of clinical surgery at La Pitié Hospital, both members of the French Academy of Medicine, for a consultation at Manet’s home in

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Paris. The two surgeons decided that amputation of the left leg was necessary and urgent, and this was carried out, one week later, at the painter’s home, under anesthesia with chloroform. However, his condition did not improve. Rackled with fever chills, Manet suffered stoically while the world of art came to pay a final visit. A medical bulletin was regularly posted on the front door of his house.5 His sister-in-law, Berthe Morisot, described the two days he took to die as unbearable. On April 30, at 7 o’clock in the evening, Manet died in the arms of his son all the while complaining about pain in his absent leg.6

Ergot is a parasitic fungus, Claviceps purpurea, of the rye seed. It is known for its action on smooth muscle fibers (uterus, arteries), but when ingested in large amounts it causes ergotism. Known in the Middle Ages as Saint Anthony’s fire, the disease ultimately led to dry gangrene of the feet and hands. The French Littré dictionary (1865) noted: “in the presence of gangrene, the strongest antiseptics must be used; amputation is rarely successful.”9

Edgar Degas’s loss of vision: the art of adapting
To the attentive observer, the creative evolution of Edgar Degas (1834-1917) and the variety of techniques he used were clearly shaped by the course of his eye ailment, a handicap that he adroitly managed to turn to his advantage. The painter and critic André Lhote extolled “the second Degas, that of the latter years, when his failing eyes forced him to embrace the essential,”10 and for Auguste Renoir, “Degas painted his best canvases when he could no longer see.”11 Degas was treated by two of the most famous ophthalmologists of his day, Edmond Landolt and Charles Abadie, but no medical record has yet been found. It was during the Franco-Prussian war that Degas, then aged 35, became aware of a loss of vision in his right eye during firing practice. His contemporaries, notably Edmond and Jules de Goncourt, noticed that the painter half shut his eyes when looking at distant objects. This was diagnosed as myopia, a vague term, which at the end of the 19th century loosely applied to a great number of cases of “poor vision.”12 In his study Les Yeux des Peintres [The Eyes of Painters] (1999), Philippe Lanthony, an ophthalmologist who specializes in color vision at the Quinze-Vingts Hospital in Paris, has reservations about the diagnosis even though it was compatible with Degas’s habit of painting subjects close up (and his horror of painting in the open air). Examination of the glasses prescribed by Landolt (now in the Orsay Museum) revealed only a small correction of 1.5 diopters. The hundred or so portraits of Degas show him wearing glasses outside only twice and never when he is reading.13 According to Dr Lanthony, two diagnoses can be excluded: amblyopia, which normally does not develop at a late age, and myopic maculopathy, in which the myopia is much more severe.12 The very special lighting and the representation of space in Degas’s work suggest monocular vision; this defect in the perception of depth could also explain the frequent presence of mirrors in his paintings.

In November 1871, writing to his friend James Tissot, Degas described a sudden loss of vision in his left eye: I recently suffered, and still do, from a sudden weakening and disorder in my eyes. It began beside the lake at Chatou under a bright sun while painting a watercolor. And it made me lose three weeks, during which I couldn’t read, travel, or even go outside.14 The clinical details are precise: sudden loss of vision, a disorder resolving spontaneously in a few weeks, and absence of other clinical signs (pain, watery eyes, edema). Degas’s ophthalmic disorder developed progressively, with loss of sharpness of vision, photophobia (circa 1873), scotoma (circa 1884), and reduced color vision (circa 1895).

His eyes saw only one part of an object at a time; planes were cut up like a trellis (…) He saw some parts very clearly while others were a complete blur (…). He told a young painter, Maurice Denis, I see your nose, but I do not see your mouth.”12
Despite considering himself nearly totally blind (he had his newspaper read to him by his housekeeper), Degas nonetheless continued his social activities: visits to the Opera, journeys to Spain and Morocco (1889), participation in and organization of impressionist exhibitions. Similarly, his production of paintings was considerable up until 1895. Working in semidarkness, wearing glasses with strongly tinted lenses, Degas used magnifying glasses to examine photographs and drawings that he enlarged himself by successive tracings and used for painting. His last portraits (Renoir, Mallarmé, Halévy, Rouart) were all painted from enlarged photographs.\textsuperscript{12,13}

Some people even went so far as to doubt whether Degas really had poor vision, like Claude Monet, who considered him a “joker,” or the art dealer Ambroise Vollard who said, “Degas pretended not to see in order to avoid being obliged to recognize people.”\textsuperscript{14} Even his brother was a doubter: “He does not suffer from any disease, except deafness.”\textsuperscript{15} However, Degas’s productivity and social activity declined after 1895; he then began modeling statuettes, which gave him a better perception of three-dimensional objects thanks to the sense of touch. Degas noted: “My infirmities have prevented me from continuing to paint with oils, so I have to be satisfied with pastels.” By adopting this technique and using bright colors, he could carry one, but he finally had to give up when he could no longer see them.\textsuperscript{15} The diagnosis of retinochoroiditis was put forward by the painter Maurice Denis who suffered from the same condition; today this hypothesis seems the most probable.\textsuperscript{16}

\textbf{Auguste Renoir: “one does not need hands in order to paint!”}

The first symptoms of polyarthritis struck the painter in 1901. His hands with their protruding bones beneath the wrinkled skin had fingers that were twisted forward and wrapped in tight bandages to prevent the nails from penetrating the palms. The first phalanx of the right thumb was bent back, having been dislocated and badly reduced. It was separated from the paintbrush inserted between thumb and forefinger by a thin corn plaster. It was under such conditions that Renoir painted during the last years of his life, without being the least discouraged, with the same passion as in his youth, the same love of life, the same fervor, and the same enjoyment.\textsuperscript{16} Renoir was treated with antipyrine, an analgesic much in fashion at the start of the 19th century. He also took the waters at the spa towns of Bourbonnes-Bains and Aix-les-Bains. He consulted the famous Doctor Gachet, physician and “protector” of Honoré Daumier, Vincent van Gogh, Édouard Manet, Armand Guillaumin, Paul Cézanne, Gustave Courbet, Claude Monet, Alfred Sisley, and Camille Pissarro.\textsuperscript{17}

When his art dealer, Vollard, visited him in Cagnes, Renoir declared, “As you can see, hands are not needed for painting! The hand, it’s a lot of nonsense.”\textsuperscript{15} His son, the filmmaker Jean Renoir, noted in his memoirs that from 1911 on his father was not mobile, even with the aid of crutches. Contrary to legend, the paintbrushes were not fixed to his hands, simply his palms were protected by a gauze bandage and talcum powder. Every day, Renoir was carried from his bed to his wheelchair and settled in front of his can- 

A lover of bright tints (cinnabar, Naples yellow, ultramarine), Renoir naturally used numerous metallic pigments. A chain-smoker, he rolled his own cigarettes, unaware that each time he deposited the toxic compounds of his paint-impregnated fingers on the cigarette paper. In fact, 0.05 mL of red cinnabar contains 100 to 150 mg of mercury sulfide, and repeated inhalation several times a day would be 100 times more toxic than the official toxic limit of mercury permitted in the air (0.01-0.1 g/m$^3$). Painters ingested metallic pigments by smoothing their paintbrush with their mouth, and by drinking, eating, and smoking without washing their hands. The drying of clothes stained with paint and the burning of old canvases in the stove also gave off toxic metallic vapors.\textsuperscript{18}

In 1988, two doctors and two professors of the Copenhagen School of Fine Arts published in the \textit{Lancet} a study that established a correlation between the onset of certain rheumatic diseases in painters and intoxication by metallic pigments (cobalt, copper, manganese, lead, chromium) present in certain bright colors. The Danish authors compared the use of colors in two paintings by Claude Monet with the palette of Renoir. Thus, in the \textit{Skaters in the Bois de Boulogne} (1868) and in the \textit{Woman with Umbrella} (1875), Monet used very few bright colors such as blue, red, and yellow. The dominant colors were gray, olive green (iron silicates), ochre (iron oxide), blue gray and black (bone), which contain very little or no toxic heavy...
metals. The same comparison can be made with Edgar Degas who used more pigments containing iron and carbon than his contemporary Renoir who was very exposed to heavy metals (mercury, arsenic, cadmium, tin, antimony, cobalt). The authors showed that heavy metals that entered the organism induced enzymatic inhibition, denaturation of proteins, or immunosuppression, all pathophysiologic processes implicated in the onset of certain rheumatologic diseases.

Vincent van Gogh: a victim of pathologists?

Vincent van Gogh (1853-1890) was the son of a Calvinist preacher, and three of his paternal uncles were art dealers. The life of the painter was punctuated with tragic adventures and dismal experiences, which led to him killing himself with a bullet to the thorax on July 27, 1890 in Auvers-sur-Oise, where he was being treated by Doctor Paul Gachet. His physician was a cultivated art collector and depressive freethinker, who was infatuated with psychiatry and a mediocre practitioner. van Gogh’s tragic end contributed to the legend of the artist who had painted 44 self-portraits and kept up a regular correspondence with his younger brother Théodore, who died in the Utrecht asylum one year later.

It all began with the “drama of the excised ear.” At Arles, on the evening of December 23, 1888, Vincent van Gogh went up to his room in the Yellow House, sharpened his razor, and cut off the lower half of his left ear. He then covered his head with damp towels and a bonnet, wrapped the piece of ear in paper and went to a brothel in the rue Bout d’Arles where he frequently visited a certain Rachel. He found the young girl, offered her his grisly present and declared: this is a souvenir of me, look after it carefully. Rachel immediately fainted. The next morning, van Gogh was found unconscious at his lodgings, his head wrapped in bloodstained towels. Agitated and menacing when awoken, he was taken to Arles Hospital and put in a padded cell. The amputated ear was collected by a policeman, and the intern, Félix Rey rapidly sutured

Some metallic pigments used in painting

Known in Egypt around 8000 years BC, certain metallic salts (mercury, copper, arsenic, tin, iron) mixed with linseed oil, which forms nearly 80% of the pigment. From the Roman Empire to the Renaissance, new metals were used as pigments (lead, antimony, cobalt, chrome, cadmium, manganese, aluminum).

- Cinnabar: a red vermilion color, derived from mercuric sulfide (HgS).
- White lead: white pigment composed of lead carbonate (2PbCO₃; Pb(OH)₂).
- Bright yellow: cadmium or lead sulfide (Pb CrO₄).
- Naples yellow: prepared from lead antimonate (Pb₃(SbO₄)₂).
- Violet: prepared from manganesian ammonium phosphate and cobalt arsenate.
- Verdigris: copper acetate.
- Cobalt blue: composed of cobalt oxide and alumina (CoO; Al₂O₃).
- Ultramarine: aluminum-based (Na₆-10 Al₆ Si₆ O₂₄ S₂-4).
- Oxide blue: prepared by exposing silver strips to a mixture of salt, vinegar, alkali, and alum.
the missing part back into place, and the wound healed without complications. On January 7, 1889, the intern noted in the discharge register: “A form of epilepsy characterized by hallucinations and episodes of confused agitation that were precipitated by alcohol excess.” During his stay in Arles, van Gogh had been encouraged by Paul Gauguin to consume quantities of alcohol and to frequent the bordellos. Having gone to Provence in the hope of founding a painting workshop like the school at Pont-Aven (where Gauguin had been a leading light), van Gogh had been profoundly disappointed by the hostility of Gauguin to the project. The two men had separated on bad terms a few days before the “drama of the severed ear,” whose versions are as numerous (and contradictory) as the hypotheses explaining the event.27,19,21

On May 8, 1889, van Gogh was interned, at his own request, in the Saint-Paul-de-Mausole Asylum at Saint-Rémy-de-Provence. For one year he enjoyed the tranquillity and the comprehension of the nuns and personnel of the establishment. Appreciating the quality of the light and the glowing beauty of the setting (the asylum is a jewel of Provencal Romanesque art), van Gogh produced nearly 150 paintings and drawings, including Irises and Vincent’s Room in Arles. This year spent in Saint-Rémy is considered one of the important creative periods in the oeuvre of Vincent van Gogh.

The first diagnoses of the painter’s neuropsychiatric disorders were made by Doctors Rey and Urpar (Arles) and Peyron (Saint Rémi), who suggested epilepsy with visual and auditory hallucinations associated with acute mania with generalized delirium.25 Gachet spoke simply of unwise exposure to the sun plus chronic intoxication with turpentine and camphor (with which he impregnated his pillow in order to find sleep). Numerous other hypotheses by a host of doctors followed: cerebral tumor (Bader), psychomotor temporal epilepsy (Gastaut), schizoid syphilis (Eichbaum), precocious dementia (Bychowski), degenerative psychosis (Hutter), Ménière’s disease (Yasuda then Arenberg and colleagues), tuberculous meningencephalitis (Dupinet), thujone intoxication (Arnold), schizophrenia (Kahn et Jaspers), melancholia (Michel).21-25

It seems that van Gogh was treated for psychomotor epilepsy with extracts of digitalis, and some believe that the intoxication could explain the visual disorders like dyschromatopsia and xanthopsia, and hence the painter’s trademark yellow suns surrounded with circles and haloes, and the extraordinary yellow of the cornfields.26 In the two portraits of Doctor Gachet, van Gogh depicted a flower of the purple foxglove (Digitalis purpurea). Other “pathobiographies” attribute the chromatic particularities of the painter’s palette to cataract, corneal dystrophy, or glaucoma (Maire).21,22 In a work devoted to van Gogh, Professor Henri-André Martin, painter, otorhinolaryngologist, honorary professor at the Lyon Faculty of Medicine, concluded: It is wrong to want to understand everything and resolve van Gogh like an elementary mathematical problem. It would be unseemly to want to inflict a positivist analysis on his person and on his work.20

**Henri-Marie de Toulouse-Lautrec: the misfortunes of the “little chap”**

The Montmartre painter Toulouse-Lautrec (1864-1901) suffered all his life from his ungracious appearance. When about 8 years old, his weak health and multiple fractures had already given him a close acquaintance with doctors and spas. A victim of all kinds of abuses, he died aged 37, worn out and in despair.

His father, Alphonse de Toulouse-Lautrec Montfa, descendant of Raymond IV, Count of Toulouse, and his mother Adèle Tapié de Céleyran were first cousins. Henri-Marie was born on November 24, 1864, in the family mansion of Bosc situated on the ramparts of Albi. The baby seemed so healthy that he was nicknamed “lou poulit” (patois for little beauty) and because of his insatiable appetite he was deemed worthy of the “legendary Lautrec stomach.”27,20

In 1872, Toulouse-Lautrec studied at the Lycée Fontanes (now Condorcet) in Paris — where his pals called him “little chap.” He then suddenly began to suffer from unexplained feverish attacks with severe pains in the knees and hips. On the advice of doctors, he began taking thermal cures at Amélie-les-Bains, Plombières, Lamalou-les-Bains, Evian, Guyon, and Barèges, accompanied by his mother. In March 1877, he was subjected to an “electric brush treatment” that had previously cured his uncle Charles.30

In Albi, on May 30, 1878, Toulouse-Lautrec slipped, fell, and fractured his left thighbone. The family doctor set the limb with a plaster cast. After one month of immobilization and an equally long convalescence, he could only walk lopsidedly, “like a duck,” as he noted in a letter to a friend. A Toulouse-Lautrec does not walk with a cane! roared his father when he happened to notice the instrument unworthy of the sporting reputation of the family (to the great despair of the count, his son had never mounted a horse). During the holidays in July 1879, at Barèges (Hautes-Pyrénées) while walking with his mother, he slipped into a ravine and fractured his right thighbone; another immobilization, another convalescence. From
that date on, his growth suddenly slowed. His lower and upper limbs ceased to grow even though his trunk gained 5 cm. When 20 years old, in 1884, Toulouse-Lautrec was only 5 feet tall, about one inch less than that required for military service (decree of November 30, 1872). The average height of conscripts in 1885 was about 64 inches. He was already what would later be called: the “greatest dwarf of the century.”

In addition to his small size, Toulouse-Lautrec’s physical appearance was unsightly: he concealed his vast head beneath a large hat and hid the hypoplasia of his lower jawbone with an abundant beard. He also had to wear glasses in order to paint. Yvette Guilbert, his favorite model, described him thus:

He was small in size, had an enormous brown head, a heavily colored face and black beard, greasy, oily skin, a nose big enough for two people, with a mouth slashing the face from one side to the other, and pinkish-violet, flat and flabby lips that lined his fearful orifice.

Toulouse-Lautrec sketched his muse as he saw her: because he had exaggerated her scrappiness and pointed nose, Yvette Guilbert revenged herself by calling him “the little monster,” without realizing it was the artist’s talent that would save her from oblivion.

The etiology of the disease remains hypothetical. The consanguinity, the bone fragility, the late and unequal bone growth, and the craniofacial deformations are the main characteristics of Toulouse-Lautrec’s disease. After having eliminated the diagnoses of premature puberty and rickets, biographers unanimously class the disease among the genotypic chondrodystrophies. In the absence of x-rays and biological or genetic examinations, the retrospective diagnoses are as follows:

- osteogenesis imperfecta (Seedorf - 1949),
- achondroplasia (Séjournet - 1955),
- Morquio’s disease (Lévy - 1957),
- multiple epiphyseal dysplasia (Flament - 1965),
- pyknodysostosis (Marotteaux and Lamy - 1966),

Today this diagnosis is the unanimously accepted diagnosis. Séjournet, the biographer of Toulouse-Lautrec, wrote, “Like Goya, like Ensor, he draws from his despair a force against the destiny that isolates him. Thus to our eyes and forever, his paintings: Mélinite (an explosive), Jane Avril, cabaret dancer; La Goulue (The Glutton), Louis Weber, lead dancer at the Moulin Rouge; Grille d’Égout (The Sewer Grating), a dancer with terrible teeth; Valentin le Désossé (The Boneless One) male dancer; seem to echo the pathetic and derisory vortex of his own dance with death.”
The Dufy "miracle"

Raoul Dufy (1877-1953) suffered his first arthralgias in childhood. His rheumatoid polyarthritis developed slowly from 1935 until 1948, when his functional disability was already well advanced. He was treated with injections of gold salts, underwent vertebral manipulations, and was treated at spas in Spain. In 1948, he suffered very intense articular pains in the wrists, knees, and ankles. However, he could still use his left hand. He has not lost his subtle touch with lines or his fine strokes. “He draws with a pencil, and just lightly strokes the paper, using his right hand as a support,” noted his friend Pierre Courthion, a well-known art critic.35

Since he used bright colors in his work, the painter was also a great consumer of metallic pigments. Dufy, as everyone knows, is one of our greatest colorists. He has the magic touch. It is his favorite form of expression, and it takes precedence over all the other forms, which explains his novelty. Color gleams in his work, light spreads out with a richness, warmth, and life that are comparable, in their own way, to the colors of Veronese and Rubens that Delacroix so admired. Everything is fresh, alive, clear, joyful as the spring in nature or youthfulness in life,

wrote Pierre Camo in 1947 in his Dufy the Enchanter.36 The following year, Jean Cocteau wrote a pamphlet on the painter and reminisced on his intense physical suffering:

He had the appearance of a red devil always ready to emerge from a green box. Since then, we have each grown older in our own corner and in our own way. Dufy became an invalid who fought, and this battle with evil replaced in a way the youthful ardor.35

On April 11, 1950, the painter, almost bedridden, embarked for Boston to consult Doctors Homburger and Bonner of the Jewish Memorial Hospital. Raoul Dufy was already famous on the other side of the Atlantic, and his photograph had appeared in Life Magazine. Homburger and Bonner had noted the deformed joints and suggested he should come to the United States and be treated with a “revolutionary” therapy.36 Several days before his departure, Dufy wrote a poem that could be considered his artistic legacy:

“Tomorrow, I sail to Boston in search of my hands…” He also painted a superb bunch of brightly colored flowers entitled Cortisone (which harks back to the flowers painted by Auguste Renoir on the morning of the day he died). That same year, 1950, Philip Hench, Head of the Department of Rheumatic Disease at the Mayo clinic in Rochester, received the Nobel Prize for Medicine or Physiology for his discovery of the hormones of the suprarenal cortex (cortisone and adrenocorticotropic hormone [ACTH]), together with their structures and biological effects. He shared the prize with the biochemists Edward Calvin Kendall and Tadeus Reichstein, professor in Zurich and Basel.

At the beginning of June 1950, Raoul Dufy began a series of injections of 100 mg per day of cortisone acetate for 3 weeks. On his return to France at the end of July, he took cortisone by mouth at the dose

Yesterday the invitation arrived
Drawing me to Dr Homburger
And his hospital in America.
Tomorrow I sail to Boston in search
Of my hands.
Forty years ago I painted with Braque
at l’Estaque.
The cubist edges cut too deep into
my palette
And I joined Matisse and became a Fauve.
I covered my canvases only with the
colors that I could feel
Avoiding those that I couldn’t see.
Unsatisfied I traveled to Munich,
Normandy, Marseille
Saw the terrible women of Avignon
And found myself on the Riviera in Vence.
Fifteen years ago the attacks began.
Disfiguring my hands
As if I were painting with leaden gloves.

I sought gold
Injections. Underwent spinal
manipulations
And made a pilgrimage to a Spanish spa.
Yet my hands grew
Still.
I continued studies in my mind
Waiting for the time
When my brush could be awakened
To decorate the canvas
With arabesques and flourishes.
I have long tried to capture
The motion of race horses and regattas
The movements of the orchestra
As musicians chase the notes
In concertos of yellow and red.
I have painted Electricity
With dynamos and electrons moving
at the speed of light.
Craving more speed I released my canvases

To color silk scarves and dresses
And finally saw my work sail with the
wind.
Now my hands are splinted
And I have become disjointed
An old man whose hands will not obey
his heart.
Rheumatism loosened Renoir’s brush
from his grasp
And his son bound the bristles to the
hollow of his hand.
But Dr Perles has assured me
That the new remedy, cortisone and ACTH,
Will release the bonds
Of the arthritis that have held me in place.
My only wish: to draw freehand
Following the wind
Flowers that beckon me
And capturing them
In a vase of Anemones.
of 100 mg twice a week.37,38 Dufy also received ACTH, but the form and dosage are not known. To express his thanks, Dufy painted the portrait of the American Doctor Freddy Homburger, his “savior.”

Despite the occurrence of secondary complications, Dufy benefited very rapidly from the revolutionary treatment: he was again able to move around on his crutches, draw, squeeze the tubes of paint by himself, and renew work on abandoned canvases such as Amphithrite begun in 1935.43,47 Fully aware that he had benefited from a “therapeutic miracle,” Dufy wrote: “Is it a rebirth or a swan song?” Indeed, he was to suffer from many complications, such as abscess at the injection site, diarrhea, and severe stomachache.39

Raoul Dufy died on March 23, 1953, in his house at Forcalquier (Haute Provence Alps) of intestinal hemorrhage probably related to corticotherapy.

REFERENCES


HYGIE CONTRE POLYMNIE : DES MALADIES DE QUELQUES PEINTRES FRANÇAIS

Comme tous les hommes, les peintres ont souffert de maladies: les unes survenant selon les lois du hasard ou de la génétique, les autres étant liées à leur activité artistique (maladies « professionnelles »). L’emploi répété de solvants organiques et de pigments contenant des métaux lourds ou des substances délétères ont probablement généré quantité de pathologies par intoxication (alors inconnues). La survenue d’une maladie chez un artiste brouille inéluctablement sa perception au monde; ce bouleversement prend toute son importance pour le peintre qui restitue ses impressions et ses sentiments par des techniques plastiques. Troubles psychiatriques, malvision, affections neurologiques, maladies artériocèles, syndromes douloureux constituent des événements susceptibles de transformer, modifier ou interrompre une œuvre. Parmi les peintres français, plusieurs d’entre eux furent affectés par des maladies qui influencèrent peu ou prou leur production artistique. On peut citer les exemples d’Edouard Manet (ataxie locomotrice), d’Edgar Degas (troubles de la vision), d’Auguste Renoir (polyarthrite rhumatoïde), de Vincent van Gogh (troubles du caractère), d’Henri de Toulouse-Lautrec (pynodysostose ?), de Raoul Dufy (polyarthrite rhumatoïde). Pour autant, les différentes pathobiographies présentées montrent que la maladie ne fut jamais un obstacle à l’expression du génie artistique; au mieux, le peintre s’adaptait à sa pathologie en trouvant de nouveaux moyens pour exprimer son art, au pire, il disparaissait prématurément en profitant de sa courte vie pour faire explorer sa créativité.
In the lovely cemetery in Auvers-sur-Oise stand two graves, leaning against the wall. They are covered with a mantle of ivy giving the impression that there is in fact just one grave. Only the simple inscriptions on the gravestones and the rather sad bunch of plastic sunflowers indicate that under this little corner of soil and sand facing the gentle valleys of the Oise lie the remains of Vincent van Gogh and his brother Theo. Auvers is only 30 kilometers north of Paris, and it was to this village set in the peaceful countryside that Vincent van Gogh arrived by train on May 21, 1890. It was here, too, 70 days later, on July 29, that he died in the arms of his brother. During this short period of time, Vincent produced 77 paintings, some of which feature among his most important works, as well as 30 drawings and an engraving.

Grief-stricken, Theo died six months later in Utrecht, on January 21, 1891. His widow, Johanna requested that Theo’s remains be buried alongside his brother’s in the graveyard of this charming French village. His ashes were in fact transferred to Auvers-sur-Oise in 1914.

View of the charming village of Auvers-sur-Oise, which lies to the north of Paris in the valley of the river Oise. It was here that Vincent van Gogh spent the last few months of his life. The village itself and the surrounding countryside provided van Gogh with inspiration for some of his most famous paintings. The Oise region was in fact much frequented by painters in the latter part of the 19th century. In particular, Cézanne painted a view of the village. © Moulu/Sunset.

Just 30 kilometers (19 miles) from Paris lies the pretty valley of the Oise where Vincent van Gogh spent the last weeks of his life before committing suicide. After mutilating his ear on December 24, 1888, he entered the Saint-Paul-de-Mausole Asylum in Provence where he spent nearly one year. He had only one wish: to flee the heat and blinding sunlight of the south for the milder climes of the north. This he managed to do thanks to his brother Theo, who recommended him to a physician—Dr Gachet—who could look after him in the attractive little village of Auvers-sur-Oise where he had a house. Vincent arrived on May 20, 1890 full of enthusiasm for this peaceful, verdant region. He thought it was just the place he needed and threw himself into his work with zeal. But the respite did not last long. After alternating between moments of great happiness and periods of profound anguish, Vincent finally shot himself in the chest on the afternoon of July 27, 1890, and died in the night two days later in the arms of his brother. During the 2 months he spent at Auvers, he did about 30 drawings, one engraving, and 77 paintings, out of the 879 that have been attributed to him. The Portrait of Dr Gachet, The Church at Auvers, Daubigny’s Garden, and Wheat Field with Crows, are essential landmarks in the history of painting.
Steeped in memories of its famous adopted son

In the village, each alleyway, each meadow, and each empty lane, seems to recall the passage of one of the greatest painters of the 19th century. “It was at this window on the first floor that Vincent painted his only painting of the interior,” explains Maryvonne Grandfils, who shows visitors round the Auberge Ravoux, an unpretentious building where the artist rented a garret. It was here, under the rooftops, after a night and day of agony, that he died in his little iron bed. On the afternoon of July 27, 1890, in a field of wheat and under a burning sun, van Gogh shot himself in the chest before dragging himself back to the inn to die.

Today, 125 years later, on a beautiful September afternoon, Madame Grandfils, the faithful and respectful guardian of the memory of this vulnerable person whose life she knows by heart suggests we walk round the village and the surrounding countryside, before introducing us to the intimacy of the upstairs garret that has been faithfully restored to give the impression that Vincent has just left it. “Make the most of the beautiful light, go wherever your feet lead you,” she advises. “Don’t hesitate to enter the little wood, you will find a quite charming walk.” She is right. The locality exudes calm and peace. Especially off-season, this pilgrimage is a must. One almost wonders whether van Gogh, a Dutchman, has not been adopted as a son of the village given the many tributes that are paid to him.

The village and the paintings: mirror images

First of all there are the panels to which his paintings are fixed. They are to be found everywhere in the village, in the main street, and at vantage points. They show exactly where van Gogh’s canvases were painted, allowing the person viewing to contrast the reality with the artist’s interpretation, like an art history lesson in front of the original subject. The panels are located in front of the church, opposite the town hall, and facing Daubigny’s Garden, and are all examples of the chromatic intensity and swirling touch of the “man suicided by society” as Antonin Artaud described him. The poet had been in a state of ecstasy before the work of van Gogh at an exhibition in the Musée de l’Orangerie in Paris in 1947. Artaud was fascinated by “the most genuine painter of all painters, who did not paint lines or forms, but inert natural things that seem to be in a state of violent convulsion.” It is this representation of the world that confronts the visitor each time he or she comes across one of these metallic panels and tries to work out the viewing angle and the position of the easel, and looks for differences between the painting and perspective, until finally one is won over by the “bludgeon with which van Gogh never ceases to strike all forms of nature and objects.” In his paintings, reality is transformed by anguish, by the fundamental anxiety of all beings confronted by an object. Even the most innocent view of a tumbledown cottage could conceal a secret. The church, peaceful on its hilllock, seems twisted in the painting by a mystical force. It vibrates with an internal light against a background of a tortured, almost black, sky. The town hall proudly displaying its red, white, and blue flag for the 14th of July celebration becomes, in the hands of the painter.
a sinister scene, the representation of infinite solitude in this square with its pennants drooping sadly between two spindly trees. This is the state of abandonment that the artist must have felt in this peaceful village where he continued to fight against the demons he thought he had got away from after his year at the Saint-Paul-de-Mausole Asylum in Provence.

**A safe haven from depression?**

It was to escape from the blinding light of the south of France that he had taken refuge in this village in the clement Oise valley. But to no avail. Even the innocent *Daubigny’s Garden*—“one of my most sought-after canvases,” he wrote to Theo around July 23, 1890—was metamorphosed under his paintbrush into a series of disturbing convolutions among an overabundance of flowers. “Everywhere,” according to Artaud, “the landscape paintings reveal their hostile tones, their anger at being disemboweled.” Above the village, it is finally the *Wheat Field with Crows* that greets the visitor. The place has not changed. No building has come to disfigure the plot of ploughed land. Even though we know today that this canvas is not the last one painted by van Gogh, there is no denying that references to his suffering are everywhere in the dramatic portrayal of this landscape that at first glance seems innocuous. “There are vast fields of wheat beneath a tortured sky,” Vincent wrote to Theo, “and I did not need to look far to capture the extreme sadness and loneliness.” Each stroke of his paintbrush breathes disquiet, the aberrations of a lost man. Beyond the more or less fan-
ciful interpretations that this painting attracts, it nonetheless undoubtedly conceals a few symbolic keys including the three tracks that disappear in three different directions, all without an exit. Does this reflect the point of no return that van Gogh had reached? This is entirely possible. Then there are the crows painted, in the words of Artaud, “truffle black, rich banquet black.” Birds of ill omen that “did not open the door to posthumous glory,” but which allowed him to open “…the door…to an enigmatic and sinister afterlife.”

Though the fields have changed little since van Gogh knew them in the summer of 1890, the reputation of this tortured man has changed dramatically. It was a broken painter who stepped down onto the railway platform on May 20, 1890, a hard-up artist who, in his life, had sold only one single painting, The Red Vineyard, for 400 francs, but whose works today are among the most expensive on the market.

The 427 million francs paid in New York on May 15, 1990, for the Portrait of Dr Gachet painted 100 years earlier, from June 3 to 5, 1890, seem indecent when one remembers the misery of the painter’s existence. The price makes a mockery of the measly 150 francs a month that Theo managed to scrape together as a kind of allowance for his brother—a more than modest sum that the painter did not always receive and for which he felt guilty, especially after Theo became the father of a son, Vincent, born on January 31, 1890, and was having difficulty feeding his little family.

The controversial Doctor Gachet

The main figure during the painter’s last few weeks was Dr Gachet, a rather strange character. An eccentric practitioner, he befriended the numerous impressionists who lived in the Oise area and collected their works. He was also a painter in his spare time, and signed his few inferior works “P. van Rysel.” Initially, Theo had hoped that a mutual friend, Camille Pissarro, would be able to look after his brother. However, married, with six children, and having just lost his mother, and himself unwell, Pissarro felt he could not take on someone who needed a lot of attention and was often subject to violent attacks. So, instead, Theo recommended Dr Gachet who had a medical practice in Paris and a house in Auvers-sur-Oise, a favorite spot for painters and Parisians in search of green fields. Since April 1889, Vincent had dreamed of leaving the asylum at Saint-Rémy-de-Provence where he had stayed for one year. He wanted to get back to work as quickly as possible after his last attack, and take advantage of a period of calm. “I am sure that in the north I will recover rapidly, and will be well for at least some time, even though I may relapse in a year or two.” He encouraged Theo to write to Gachet, and, to speed things up, even suggested what should go in the letter: “My brother would very much like to meet you..., he hopes you will approve of his spending several weeks in your village where he wants to do some studies. He is sure he will get on well with you, and believes that his return to the north will benefit his illness, whereas a longer stay in the Midi would risk harming his health.”

On May 20, his wish was granted and he finally met Dr Gachet. After an exhausting journey, he had arrived in Paris three days earlier, on May 17, weighed down with about 60 pounds of luggage and impatient to see Theo again, and to meet Johanna, his sister-in-law, and of course little Vincent, now 6 months old. He made a good impression on Theo’s young wife, but could not stand the noise and bustle of the city for long. After remaining shut in for a whole day in the apartment at 8, Cité Pigalle, while he contemplated his paintings spread out on the floor, he agreed the following day to visit his brother’s stock of paintings, where the works of Guillaumin, Gauguin, and Russel were piled up with his own. The two brothers also visited an exhibition at the Salon du Champ-de-Mars, then the time came for Vincent to leave for the countryside exhausted. He finally arrived at Auvers with three paintings under his arm and a letter of introduction for the doctor whom he found “rather eccentric.” This first impression is even rather reserved, since he wrote to Theo that the doctor “appeared to be afflicted at least as seriously as I am.” Full of “black, black antiquities,” his large white house built at the foot of a chalk cliff did not impress Vincent either. Was it by prudence, the need for independence, or for reasons of economy that he opted to take a room at the Auberge Ravoux that was cheaper, only 3.50 francs per day compared with 6 francs, and was further away from Gachet’s house than the inn at Saint-Aubin that the doctor had recommended?
Solace in a frenzy of paintings

Though he was seduced by the village and its “many thatched roofs, which is becoming rare,” and by the region “…it is extremely beautiful, a typical picturesque open countryside,” his relations with Gachet were not what he had hoped for. “I cannot rely on Dr Gachet at all,” he wrote several weeks after his arrival. Yet, to begin with, he thought he could make a real friend of this old man who loved art and seemed to have known Manet, who had discovered the works of Monet and Renoir at the Impressionist Exhibition of 1874, and who also had a long friendship with Pissarro. Cézanne regularly visited Dr Gachet’s house in 1873 during the year he spent at Auvers with his partner and son, and later Guillaumin. Having been plunged into grief by the death of his wife in 1875, Gachet was a sad person “with a haggard face.” However, van Gogh adapted to the doctor. He even followed some of his recommendations: going to bed at 9 o’clock, getting up at 5 o’clock, and warding off the return of attacks by hard work. Gachet let Vincent use a printing press he had in his attic to etch a self-portrait he was working on. Vincent also lunched with Gachet every Sunday and sometimes on Mondays or Tuesdays to finish a canvas of Marguerite at the Piano, the doctor’s daughter, or of his daughter in their garden. He also decided to do a portrait of Gachet, and was only too happy to have a model who actually wanted to pose. The painting shows the doctor with “a white cap on his head, light-colored, and very prominent, the hands in clear flesh tints, and wearing a blue tail coat, against a cobalt background.” More than a portrait, it is a manifesto, a kind of social icon, whereby van Gogh expressed the misfortune that haunted this disillusioned and sad human being. The features transcend those of just the doctor. “I want,” explained Vincent, “to paint portraits that one century later people will view as apparitions. I now have a portrait of Dr Gachet bearing the heartbroken expression of our time.”
painting showed him “leaning against a red table on which there is a yellow book and purple foxglove” (in homage to his interest in homeopathy). Gachet loved the portrait so much that he immediately asked Vincent to paint another one for him. This second painting is today in the Musée d’Orsay in Paris, thanks to the donation made by Gachet’s son in 1949, while the first painting was sold by Christie’s.

The tragic climax

At about this time, van Gogh’s reputation was starting to be established through the efforts of Theo. Several artists including Guillaumin wanted to exchange canvases with him. In a very laudatory article, the art critic Albert-Émile Aurier thanked him for a work painted at Saint-Rémy-de-Provence. But the praise fell on deaf ears, all Vincent wanted was for his brother and family to come and live near him in the country. On June 8, they all arrived after being invited to lunch by Gachet. It was a beautiful day, Vincent was in relaxed mood and played with his little nephew, showing him the hens and ducks. The happiness he dreamed of was within his reach. But not for long. Several days later, little Vincent became ill and nearly died. Anxious and himself short of money, Theo made it clear to his brother that it was becoming more and more difficult to provide the monthly allowance. He invited him to come to Paris on July 6 to try to find a solution, and to introduce him to Albert-Émile Aurier, and the painters Émile Bernard and Toulouse-Lautrec. But Vincent could not stand the pressure. He cut short his visit that was meant to last several days and took the evening train back to Auvers the very same day. He was devastated. Was it because he had seen his paintings decaying in the squalid storeroom belonging to the art-dealer Julien (Père) Tanguy? Was it his fear for the life of little Vincent and for his mother exhausted after nights of watching over her son? Was it the prospect of being alone for several days while Theo and his family were in Holland? Was it, above all, the prospect of having to stop painting due to lack of money? In spite of a letter from Johanna that comforted and reassured him concerning little Vincent, he did not recover from the storm that was threatening his livelihood. He did not know how to react. He felt helpless confronted

*Portrait of Doctor Gachet.* Van Gogh painted two versions of this portrait, at the request of the subject, both in June 1890. Dr Gachet, a painter himself, was a friend of several of the Impressionists and invited them to stay with him in Auvers-sur-Oise (Cézanne did a painting of his house). Vincent initially had high hopes of Dr Gachet, but came to realize that he could not rely on him. In this portrait, van Gogh captured some of the melancholic, contemplative mood to which the doctor was prone. On the table can be seen a sprig of purple foxglove, the source of digitalis. Dr Gachet was the only male sitter that van Gogh painted in Auvers. Oil on canvas, 68 x 57 cm. Musée d’Orsay, Paris. © AKG Images.

*Marguerite Gachet in the Garden.* Executed in June 1890, this was one of two paintings van Gogh did of Dr Gachet’s daughter. Oil on canvas, 46 x 55.5 cm. Musée d’Orsay, Paris. © Photo RMN - Gérard Blot.
with problems of money and reproached his brother for leaving him stranded. “My own existence is threatened at its very roots, my future too is tottering.” He could not see any way out, except to continue working relentlessly “even though the paintbrush is falling from my hands.” On July 14, Theo left Paris for Holland instead of taking several days’ rest at Auvers as Vincent had so desperately hoped. Was it the coup de grâce for this abandoned soul? We will never know. Even though on his return Theo immediately sent his brother a 50 franc note, nothing could stop Vincent from taking the fatal step.

He left his little garret at the Auberge Ravoux after lunch, took the street that runs through the village, climbed the hill, and there, alone, facing the fields, shot himself in the chest. It was July 27, 1890 and Vincent was just 37 years old. The innkeeper, seeing he had not returned for supper, was starting to worry, when Vincent finally arrived and went straight upstairs to his room. It is in this little garret under the roof with its cracked walls, splashes of grayish paint, and faithfully restored mildew that all visits to Auvers-sur-Oise end. It was here that Ravoux found the painter in agony. He summoned the doctor who lived opposite, then Dr Gachet, who administered first aid, but they decided not to remove the bullet as it was lodged just below the heart. Theo was informed in Paris and arrived panic-stricken late the following morning. Despite Vincent’s strong constitution, he was writhing “in terrible agony.” He died on July 29 at 1:30 AM leaving an unfinished letter to his brother in which he explained: “In my kind of work, I risk my life.”

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**Vase With Irises Against a Yellow Background.** This still life was painted in Saint-Rémy, in May 1890, just before Vincent left to live in Auvers-sur-Oise. He discovered the iris motif in the garden at the asylum at Saint-Rémy and produced several pictures with these flowers as the main subject during this period. Oil on canvas, 92 x 73.5 cm. Rijksmuseum Vincent van Gogh, Amsterdam. Vincent van Gogh Foundation.

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**Practical Guide to Auvers-sur-Oise**

- **How to get there**
  - By road: Take the A15, direction Cergy Pontoise, leave the A15 at exit 7, direction Méry and Auvers.
  - By train (about one hour). Leave from Gare Saint-Lazare. Change at Pontoise for Auvers.
  - Information: Tourist office: 00 33 1 30 36 10 06, E-mail: otsi.auvers@wanadoo.fr

- **What to see**
  - The Château d’Auvers. Visit with spectacle “In the footsteps of the impressionists.”
    - Tel: 00 33 1 34 48 48 45, www.château-auvers.fr
    - Auberge Ravoux, called the Maison van Gogh.
      - Tel: 00 33 1 30 36 60 60
    - Musée Daubigny. Tel: 00 33 1 30 36 80 20
    - Atelier Daubigny (workshop). Open only from Easter to All Saint’s Day (November 1).
      - Tel: 00 33 1 34 48 03 03
    - Musée de l’Absinthe. Tel: 00 33 1 30 36 83 26

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Photograph showing the gravestones of Vincent van Gogh and his brother Theo, in the cemetery at Auvers-sur-Oise. Theo died just 6 months after Vincent’s death in Utrecht, the Netherlands, on January 21, 1891. His wife, Johanna, requested that Theo be buried alongside his beloved brother, which was finally achieved in 1914 when his ashes were transferred to Auvers. © Rasmussen/Diaporama.
In van Gogh’s footsteps in Auvers-sur-Oise – Spaak

A TOUCH OF FRANCE

MEDICOGRAPHIA, VOL 27, No.3, 2005

WORK AS A TREATMENT FOR “MENTAL WEAKNESS”

No idea was more disagreeable to van Gogh than Cézanne’s belief that he would produce “the paintings of a madman.” And, in August 1889, while in the asylum at Saint-Rémy, Vincent wrote that he hated nothing more “than having to ask a doctor for permission to do a painting,” and was convinced “that if sooner or later I am more or less cured, it will be because I have cured myself by working.” Though the genius of the painter is beyond question, it is evident that this fragile person painted despite (or perhaps because of) the more or less clear-cut symptoms of his mental illness manifested by the mutilation of his ear at Arles in 1888, his repeated attacks, his confinement in the asylum at Saint-Rémy-de-Provence in 1889, and his suicide in Auvers in 1890. According to a study by Doctor Jean-Marc Boulon, *Concerning the Clinical Case of Vincent van Gogh*, the diagnoses of contemporary psychiatrists suggest “manic-depressive psychosis with acute mania with hallucinations and delusions complicated by epileptic fits that are exacerbated during periods of undernutrition, overwork, or intoxication with absinth, digitalis, potassium bromide (prescribed at Arles), camphor, and carbon monoxide, as well as by his excessive addiction to coffee and smoking.” The cause of the bipolar disorder should be looked for, as in all patients with alternating periods of euphoria and depression, in the family history and a probable genetic origin. These periods of intense depression with mutism, nonproductivity, and melancholia, that can even lead to suicide, alternate with moments of hyperactivity (also called hypomania), thanks to which van Gogh was able to create his large number of paintings and to pen his voluminous correspondence.

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SUR LES TRACES DE VAN GOGH À AUVERS-SUR-OISE

C'est à trente kilomètres de Paris, dans une jolie vallée de l'Oise que le peintre Vincent van Gogh passera ses dernières semaines avant de se donner la mort. Après avoir été interné près d'un an à l'asile de Saint-Paul-de-Mausole, en Provence, suite à la mutilation de son oreille le 24 décembre 1888, il ne rêve que d'une chose : fuir la chaleur et la lumière trop brutale du sud pour retrouver la douceur du nord. C'est chose faite grâce à son frère Théo qui le recommande à un médecin – le Dr Gachet – qui pourra s'occuper de Vincent dans le joli petit village d’Auvers-sur-Oise où il possède une maison. Le peintre arrive le 20 mai 1890 plein d'enthousiasme pour cette région paisible et verdoyante. Il pense avoir trouvé la paix et se remet au travail avec fougue. Mais, le répit est de courte durée. Alternant des moments de grands bonheur avec d'autres d'angoisse profonde, il finit par se tirer une balle dans la poitrine le 27 juillet 1890 dans l’après-midi et rendra l’âme dans les bras de son frère dans la nuit du 29. Durant les deux mois qu’il passe à Auvers il aura réalisé quelques 30 dessins, une gravure et 77 tableaux, sur les 879 qu’on lui connaît. Essentiels dans l’histoire de la peinture moderne, « Le portrait du Dr Gachet », « L’Église à Auvers », « Le jardin de Daubigny » et « Champs de blé aux corbeaux », font partie de ceux-là.
Instructions for authors

General instructions

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- All texts should be submitted in English.
- Provide 1 color photograph of main author.
- On the title page, provide: a title (concise and informative); full names of authors (first name, middle name initial, and last name); highest academic degrees [in country-of-origin language]; affiliations [names of department(s) and institution(s) at the time the work was done]; a short running title (no more than 50 letters and spaces); keywords (5-10); corresponding author’s complete mailing address and telephone No., fax No., and e-mail address; acknowledgments (on title page, or at end of main text).
- Include an Abstract of 200-230 words for all texts except Editorials and replies to the Controversial Question.
- Figures and Tables. Figures should be of good quality or professionally prepared, numbered according to their order, with proper orientation indicated (eg, “top,” or “left”). Figures may be provided as pdf files (printing resolution = 300 dpi scans, on CDrom, or via e-mail; screen resolution = 72 dpi scans acceptable only if large-sized format [A4]). Provide fully explicit legends, not repetitive of text. All abbreviations used should be explained in the legends. As figures and graphs may need to be reduced or enlarged, all absolute values and statistics should be provided. Illustrations will be reproduced in full color only when clearly necessary, eg, images from nuclear medicine or histology. Provide each table on a separate sheet, with title above and description below. All figures and tables should be cited in the text, with distinct numbering for figures and tables.
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- Include Headings using a consistent style for the various levels of headings, to highlight key points and facilitate comprehension of the text. The Editorial Department reserves the right to add or delete headings when necessary.
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