True Remission in Depression: The Ultimate Goal

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DEPRESSIVE DISORDERS CONSTITUTE A MAJOR PUBLIC HEALTH issue, and it is estimated by the World Health Organization that they will rank in second position among all diseases in terms of prevalence by the year 2010, thus contributing heavily to the global burden of disease in humans. Advances in the treatment of depressive disorders will therefore constitute a major challenge for the medical community and for society in the years to come. The concept of clinical remission in the treatment of major depressive disorders has gained growing attention in the last few years. The reasons for this relatively recent interest are severalfold: depressed patients as well as patient organizations are not totally satisfied with the current effectiveness and tolerability of available antidepressant medications. Despite the obvious benefits of antidepressants, many depressed patients still suffer from incapacitating residual symptoms, and these patients are at a higher risk of relapse or recurrence than patients who achieve full remission after antidepressant therapy. Patients who reach full remission after treatment have a better level of functioning and an improved prognosis compared with patients who are nonremitters. Adequate clinical remission is therefore of great functional importance to the patient, because it seems to be a predictor of long-term stability and a rather good indicator of better psychological functioning, the latter being of utmost importance when assessing the quality of life of our depressed patients. For the above reasons, it is becoming of great interest to the scientific community and our patients to consider not only rates of response, but also remission rates, in order to assess the real clinical efficiency of antidepressants in everyday practice and to evaluate new treatments in outcome studies. This issue of Medicographia brings together experts in the field of affective disorders to discuss from different perspectives the critical issues related to the concept of true remission in depression.

✦ H. J. Möller et al review current knowledge on the natural course of a depressive episode, symptoms that may be predictive of response and remission, and the time course of their alleviation during antidepressant therapy.

✦ D. Baldwin and A. Lopes focus on the differential effects of antidepressants on endogenous depression and depression associated with anxiety disorders, in relation to the time course of depression and the quality of remission in depression.

✦ P. Monteleone and M. Maj look at the relevance of circadian rhythm disturbances in depression and the impact that the resynchronization of circadian rhythms has on the quality of remission.

✦ C. Soldatos and C. Theilerits reflect on the quality of the sleep-wake cycle as a potential marker of remission in depression. They also deal with such issues as the persistence of sleep disruption after antidepressant treatment, and the promises of sleep-restorative antidepressants.

✦ S. Kennedy and S. Rizvi emphasize the importance of the maintenance of proper sexual functioning and quality of life in patients in remission from depression, which is also a key factor for drug compliance.

✦ J. Price and G. Goodwin analyze the impact of antidepressant therapy on cognitive and emotional reactivity after remission and the implications this has for relapse.
Defining remission in depression: the challenge of complete recovery – Mendlewicz

Keywords: remission; recovery; residual symptom; antidepressant; major depression

Definitions of remission can vary across the literature, and questions arise as to the boundary between full remission and partial remission, the presence after treatment of residual symptoms, and the return (or not) to premorbid psychosocial functioning. According to a consensus conference of the MacArthur Foundation, clinical response is defined as a period of time during which there is some improvement in symptoms, but not of enough magnitude as to represent achievement of full remission, with the persistence of some residual symptoms. On depression rating scales, this state usually corresponds to at least a 50% improvement in scores. By contrast, full remission is obtained when clinical improvement is such that the patient becomes almost asymptomatic. Clinical remission is usually defined by a score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HAM-D17) or a score of 10 to 12 or less on the Montgomery-Åsberg Depression Rating Scale (MADRS). The persistence of remission over time while on maintenance antidepressant therapy is of obvious clinical relevance, as considered in the concept of recovery.

Clinical recovery can only be defined in an individual after the persistence of remission for at least 3 to 4 months. A task force of the American College of Neuropsychopharmacology carried out a review of the literature regarding potential associated factors that may influence remission in terms of timing and stability. Among others, these factors include the type of treatment, the dose, the treatment duration, the baseline severity of depressive symptoms, the stage of treatment resistance (Treatment Resistant Depression [TRD] stage), compliance, the presence of residual symptoms observed in non fully remitted depressed patients justifies the need for research into various therapeutic strategies such as switching, augmentation, and combination therapies, including with cognitive behavioral therapy, and the search for new targets to develop novel and more efficacious antidepressant treatments. There is a general consensus among experts that full clinical remission after acute antidepressant treatment should be the gold standard and one of the priority objectives to be achieved in modern antidepressant therapy. □

E. Paykel draws a list of the residual symptoms whose presence signals incomplete remission from depression and stresses the need for longer than usual continuation antidepressant treatment, which may be aided by cognitive therapy, to avoid the risk of relapse.

C. Muñoz reviews the pharmacological mode of action and clinical benefits of agomelatine, a new melatonic antidepressant.

W. Choucha and J. F. Allilaire discuss the various clinical management approaches to treating remitted patients over the long term.

G. Fava and D. Visani advocate the sequential use of pharmacotherapy and psychotherapy to address residual symptoms in patients having recovered from depression as the best model for avoiding relapse or recurrence, and stress the implications of this method in terms of treatment planning.

J. D. Guelfi discusses the merits and pitfalls of various methods to assess remission, relapse, and residual symptoms in depression.

Unfortunately, a significant number of patients do not achieve a fully symptom-free state, and display residual subsyndromal depression or subthreshold depression. These patients have been shown to have a higher risk of early relapse into depression, lower levels of social and psychological functioning, and greater rates of physical morbidity for conditions such as cardiovascular disease and stroke, as well as higher rates of mortality. Several therapeutic strategies have been proposed to achieve remission or treat residual symptoms in patients suffering from major depressive disorder. The most frequent residual symptoms targeted include anxiety, sleep disturbances, depressed mood, work difficulties, fatigue, and lack of interest. Among such residual depressive symptoms, severe chronic current insomnia—one of the most frequently observed manifestations of sleep disturbance in depression—appears to be an important residual core symptom of depression, which may be related to the persistence of cognitive problems such as asthenia, anhedonia, trouble in concentrating, and short-term memory difficulties. The rather high manifestation of residual symptoms observed in non fully remitted depressed patients justifies the need for research into various therapeutic strategies such as switching, augmentation, and combination therapies, including with cognitive behavioral therapy, and the search for new targets to develop novel and more efficacious antidepressant treatments. There is a general consensus among experts that full clinical remission after acute antidepressant treatment should be the gold standard and one of the priority objectives to be achieved in modern antidepressant therapy. □
Définir la rémission dans la dépression : le défi de la guérison complète

par J. Mendlewicz, Belgique

Les troubles dépressifs constituent un problème de santé publique majeur, à tel point que l’Organisation Mondiale de la Santé a estimé qu’en 2010 elle pourrait atteindre le 2e rang parmi l’ensemble des maladies par ordre de prévalence, et ainsi contribuer de façon majeure à la charge pathologique globale chez l’homme. Les avancées du traitement des troubles dépressifs constitueront par conséquent un défi majeur que devront relever la communauté médicale et la société dans son ensemble au cours des années à venir. Le concept de rémission clinique dans le traitement de la dépression majeure a fait l’objet d’une attention croissante au cours des dernières années. Les raisons de cet intérêt relativement récent sont multiples : les patients déprimés ainsi que les organisations de patients ne sont pas totalement satisfaits de l’efficacité et de la tolérance actuelles des antidépresseurs disponibles. Malgré les bénéfices évidents apportés par les antidépresseurs, un grand nombre de patients déprimés qui souffrent toujours de symptômes résiduels incapacitants sont exposés à un risque plus important de rechute ou de récidive par rapport à ceux ayant atteint une rémission complète après un traitement antidépresseur. Les patients obtenant une rémission complète après traitement présentent un meilleur niveau de fonctionnement et un pronostic plus favorable par rapport aux patients dont la guérison n’est pas complète.

Une rémission clinique adéquate est par conséquent d’une importance capitale pour le fonctionnement du patient, car il semble qu’elle constitue un facteur de prédiction de la stabilité à long terme et un indicateur relativement satisfaisant d’un meilleur fonctionnement psychologique, ce dernier jouant un rôle de la plus haute importance pour l’évaluation de la qualité de vie des patients déprimés. Pour toutes ces raisons, la communauté scientifique, mais également les patients, se sont particulièrement intéressés à la prise en compte non seulement des taux de réponse, mais également des taux de rémission, afin d’évaluer l’efficacité clinique réelle des antidépresseurs dans la pratique quotidienne et évaluer les nouveaux traitements au cours d’études cliniques portant sur l’efficacité. Ce numéro de Medicographia rassemble les contributions d’experts dans le domaine des troubles de l’humeur (affectifs) qui aborderont sous des angles différents les problèmes essentiels liés au concept de rémission complète dans la dépression.


D. Baldwin et A. Lopes s’intéressent plus particulièrement aux différents effets des antidépresseurs sur la dépression endogène et la dépression associée à des troubles anxieux, dans le cadre de l’évolution de la dépression en fonction du temps et de la qualité de la rémission dans la dépression.

P. Monteleone et M. Maj décrivent l’importance des troubles des rythmes circadiens dans la dépression, et l’impact que la resynchronisation des rythmes circadiens peut avoir sur la qualité de la rémission.

C. Soldatos et C. Theleritis se penchent sur la qualité du cycle sommeil-veille comme marqueur potentiel de la rémission dans la dépression. Ils abordent également un certain nombre de problèmes liés à la persistance des perturbations du sommeil après un traitement antidépresseur, et les perspectives ouvertes par les antidépresseurs ayant la capacité de rétablir le sommeil.
S. Kennedy et S. Rizvi soulignent l’importance de maintenir un fonctionnement sexuel et une qualité de vie satisfaisants chez les patients présentant une rémission à la suite d’une dépression, ce qui constitue également un facteur essentiel de l’observance du traitement.


E. Paykel dresse la liste des symptômes résiduels dont la présence traduit une rémission incomplète et souligne la nécessité d’un traitement antidépresseur d’entretien, à laquelle une thérapie cognitive peut être associée, afin d’éviter le risque de rechute.

C. Marzio dresse un tableau du mode d’action pharmacologique et des bénéfices cliniques de l’agomélatine, un nouvel antidépresseur mélatoninergique.

W. Choucha et J. F. Allilaire discutent des différentes approches de la prise en charge clinique à long terme pour le traitement des patients ayant présenté une rémission.

G. Fava et D. Visani préconisent l’utilisation séquentielle de la pharmacothérapie et de la psychothérapie pour la prise en charge des symptômes résiduels chez les patients ayant guéri d’une dépression, la considèrent comme le modèle le plus efficace pour éviter les rechutes et les récidives et insistent sur les conséquences de cette méthode en ce qui concerne la programmation du traitement.

J. D. Guelfi réfléchit sur les mérites et les inconvénients des différentes méthodes d’évaluation des rémissions, des rechutes et des symptômes résiduels dans la dépression.

La définition de la rémission est variable dans la littérature, où sont soulevées un certain nombre de questions, notamment : la limite entre une rémission complète et une rémission partielle, la présence après le traitement de symptômes résiduels et le retour (ou non) au fonctionnement psychosocial prémorbide. Selon la conférence de consensus de la Fondation MacArthur, la réponse clinique est définie comme une période au cours de laquelle est observée une certaine amélioration des symptômes, mais d’amplitude insuffisante pour correspondre à l’obtention d’une rémission complète, et s’accompagnant de la persistance de certains symptômes résiduels. Sur les échelles d’évaluation de la dépression, cette situation correspond généralement à une amélioration d’au moins 50 % des scores. En revanche, une rémission complète est obtenue lorsque l’amélioration clinique est telle que le patient devient pratiquement asymptomatique.

La rémission clinique est généralement définie par un score inférieur ou égal à 7 sur l’Échelle d’évaluation de la dépression de Hamilton en 17 items (17-item Hamilton Rating Scale for Depression, HAM-D17) ou un score inférieur ou égal à 10 à 12 sur l’Échelle d’évaluation de la dépression de Montgomery-Åsberg (Montgomery-Åsberg Depression Rating Scale, MADRS). La persistance d’une rémission durable pendant l’administration d’un traitement antidépresseur d’entretien revêt une importance clinique évidente, dans le cadre du concept de guérison.

La guérison clinique ne peut être établie chez un individu qu’après la persistance d’une rémission pendant au moins 3 ou 4 mois. Un groupe de travail du Collège américain de neuropsychopharmacologie (American College of Neuropsychopharmacology) a effectué un examen de la littérature concernant les facteurs potentiellement associés susceptibles d’influencer la rémission quant au moment de sa survenue et à sa stabilité. Ces facteurs comprennent entre autres le type de traitement, la posologie, la durée du traitement, la sévérité initiale des symptômes dépressifs, le stade de résistance au traitement (stade de dépression résistante au traitement, Treatment Resistant Depression [TRD] stage), l’observance du traitement, la présence de conditions correspondant à l’axe I, II ou III du Manuel Diagnostique et Statistique des Troubles Mentaux 4e Édition (Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition, DSM-IV), les facteurs de stress environnemental, le degré de soutien social, la morbidité rétrospective de la maladie, ainsi que la vulnérabilité neurobiologique et génétique.

Il n’existe pas de consensus global sur la durée permettant de qualifier une rémission de réelle, mais, selon la plupart des experts, cette période doit être au moins de 4 à 6 mois pour avoir une signification clinique pour le patient. La durée de la période de rémission est naturellement une importance clinique extrême pour le patient, et est conditionnée par la poursuite du traitement antidépresseur.

Malheureusement, un nombre significatif de patients n’atteignent jamais un état asymptomatique, et continuent pendant un certain temps à présenter une dépression sous-syndromique résiduelle ou une dépression infirale. Il est démontré que ces patients présentaient un risque aggravé de rechute dépressive précoce, des niveaux inférieurs de fonctionnement social et psychologique, et des taux supérieurs de morbidité physique à type de maladies cardio-vasculaires et d’accidents vasculaires cérébraux, ainsi que des taux de mortalité plus élevés. Plu-
ieurs stratégies thérapeutiques ont été proposées pour atteindre la rémission ou traiter les symptômes résiduels chez les patients souffrant de dépression majeure. Les symptômes résiduels plus fréquents visés par les traitements comprennent : l’anxiété, les troubles du sommeil, l’humeur dépressive, les difficultés professionnelles, la fatigue et la perte d’intérêt. Parmi ces symptômes dépressifs résiduels, l’insomnie chronique sévère – l’une des manifestations les plus fréquemment observées de troubles du sommeil dans la dépression – semble constituer un symptôme central résiduel important de la dépression, qui pourrait être lié à la persistance de problèmes cognitifs, notamment l’asthénie, l’anhédonie, les troubles de la concentration et les difficultés de mémorisation à court terme. La fréquence relativement élevée des symptômes résiduels observés chez les patients déprimés n’ayant pas obtenu une rémission complète justifie la nécessité de rechercher différentes stratégies thérapeutiques, notamment des traitements de substitution, adjuvants et d’association, en particulier avec une thérapie comportementale cognitive, et l’identification de nouvelles cibles pour développer des traitements antidépresseurs nouveaux et plus efficaces. Les experts sont arrivés à un consensus sur le fait que la rémission clinique complète après un traitement antidépresseur aigu doit être la référence et l’un des objectifs prioritaires à atteindre dans le traitement moderne de la dépression.
True Remission in Depression: The Ultimate Goal

Time course of response and remission during antidepressant treatment

by H.-J. Möller, F. H. Seemüller, and M. Riedel, Germany

Major depression is a complex and inhomogeneous illness with an etiopathogenesis that is based upon multiple factors that may act at different levels (psychological, biological, genetic, and social). It is a matter of fact that one single treatment, or one single treatment approach, can therefore never be adequate for such a diverse illness. There is hope that in the near future we will be able to treat patients on an even more individual level by using genetic or brain morphologic markers. In the case of drug resistance, pseudoresistance—with special attention given to adherence—should be ruled out first. Response to treatment can occur very early, even within the first 2 weeks of the treatment course. In clinical trials, the highest response rates appear within the first 4 weeks. When, exactly, and to what extent response appears, also depends on its exact definition. Two definitions have achieved acceptance in the research community—that of early improvement (20% reduction on the Hamilton Rating Scale for Depression [HAM-D] within the first 2 weeks) and that of response (≥50% reduction of the initial HAM-D score). The first may be especially useful in monitoring early symptom alleviation due to the respective treatment, while the second may be more useful in detecting sustained changes, especially when combined with a time criterion. Both are highly predictive of remission, which is usually observed at a lower rate compared with response, but which in clinical trials surpasses the response rate from week 4 to 6 onward. Thus, response to treatment may be considered as the precursor of remission, ie, the phase inaugurating the natural healing process induced by antidepressant therapy and which, in the majority of cases achieves its goal, ie, remission, the complete relief of all symptoms.

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Keywords: major depression; response; remission; time course; etiopathogenesis

Selected abbreviations and acronyms

- BDNF: brain derived neurotrophic factor
- CRH: corticotropin releasing hormone
- ECT: electroconvulsive therapy
- HAM-D: Hamilton Rating Scale for Depression
- MADRS: Montgomery-Åsberg Depression Rating Scale
- MDD: major depressive disorder
- SSRI: selective serotonin reuptake inhibitor
- STAR*D: Sequenced Treatment Alternatives to Relieve Depression (study)
pression of four major influential levels: namely, the psychological, environmental, biological, and genetic levels. An excellent overview of the most recent concepts in our understanding of the biological mechanisms of major depression can be found in reference 2.

**Stressful life events and gene-environment interaction**

Stressful life events that occur during an individual’s lifespan influence the onset and course of major depression. In a recent paper by Kendler and colleagues, the relationship between dependent stressful life events (life events that result from the respondents’ own behavior) or independent stressful life events (events that mostly result from “bad luck”) and the onset of major depression was systematically investigated in a sample of 1898 female twins (monozygotic and dizygotic). Independent and dependent stressful life events were associated with a highly significant extent with new onset of depressive episodes, and the strongest association was observed for the dependent events. The odds for the onset of major depression in the month of a life event were 5.64 for all subjects. However, major depression can also arise without any prior life event and the vast majority of people experiencing life events do not develop depression. One reason for this might be that the impact of life on the development of an illness may be moderated by a gene-environment interaction. In 2003, Avshalom Caspi prospectively investigated why life events lead to depression in some people but not in others. In a representative birth cohort of 1037 children who had had comprehensive psychiatric assessments at the ages of 3, 5, 7, 9, 11, 13, 15, 18, and 21 years, a functional polymorphism of the promoter region of the serotonin transporter gene (5-HTT) was found to moderate the influence of stressful life events on depression. Specifically, the study revealed three major results. First, with regard to the gene-environment interaction, it was found that life events after the 21st birthday significantly predicted a new onset of depression at age 26 among carriers of an S-allele who had no history of prior depression, but did not predict onset of depression among l/l homozygotes. Second, even suicide ideation, which is always susceptible to having an underlying biological mechanism, could be significantly predicted for individuals with the S-allele but not for l/l homozygotes (Figure 1). Third, childhood maltreatment during the first life decade also significantly predicted adult depression among S-allele carriers but not among l/l homozygotes. In addition, the sole relationship between genotype and depression not associated with a life event was not significant. In summary, this model further supports the concept that genetic variants with a high prevalence in the general population probably act to “promote an organism’s resistance to environmental pathogens.”

**Monoamine deficiency hypothesis**

On a transmitter level, the monoamine deficiency hypothesis remains of extreme importance. Apart from the fact that all antidepressant agents have an effect on at least one of the monoamine transmitters (dopamine, serotonin, norepinephrine), there is also compelling evidence from the opposite direction. Tryptophan is rate limiting for serotonin synthesis in the brain. Oral tryptophan depletion does not induce depression in mentally healthy subjects, but will cause depression in patients successfully treated with a selective serotonin reuptake inhibitor (SSRI). Likewise, α-methyl paratyrosine does not induce depression in normal people, but does in patients who have been treated with a norepinephrine reuptake inhibitor. The importance of dopamine in depression is highlighted by the high comorbidity rates of depression in patients with Parkinson’s disease, the antidepressant effect of bupropione, and the depressogenic effect of dopamine depletion with reserpine.

![Figure 1. Relationship between suicidal ideation and attempts, number of stressful life events, and 5-HTT allele carrier status.](image)


**Hypothalamic-pituitary-adrenal axis**

Another possible link between life stress and depression might be the moderation of depression through the hypothalamic-pituitary-adrenal axis. Depressed subjects can show elevated plasma cortisol levels and elevated corticotropin releasing hormone (CRH) levels in the cerebrospinal fluid. Furthermore, the normal cortisol suppression response is absent in about half of the most severely depressed subjects. Consequently, antidepressant-induced remission is also associated with the reversal of the abnormal suppression test, supporting the notion of a causal relationship. Most recent research for new antidepressant agents has also focused on glucocorticoid receptor blockers, with promising preliminary results.

Higher glucocorticoid levels may also be associated with reduced neurogenesis, and have been linked to a decreased hippocampal size in patients with depression. Brain derived neurotrophic factor (BDNF), which plays an important role in neurogenesis involving neuronal plasticity, synaptic growth, and neuronal cell survival, was found to be significantly reduced in a cohort of suicide completers. Antidepressant treatment options such as...
regular physical activity, electroconvulsive therapy (ECT), or antidepressant compounds have been shown to significantly elevate BDNF levels.

- **Circadian rhythms**

Circadian disturbances occur in depression and include not only disturbances to physiological parameters (e.g., body temperature) or biological parameters such as cortisol secretion, but also mood and the sleep-wake cycle. Therapeutic treatments aimed at the regulation of these disturbances in depressed patients have been shown to have a significant impact in relieving symptoms of depression. It is not surprising given this diversity and complexity in the etiopathogenesis of depression and the pharmacological mechanisms of antidepressants that there is a broad range of possible answers to the question of which therapeutic approach is the most beneficial for the individual patient. For such a highly inhomogeneous and diverse medical condition, response and remission can hardly be achieved with only a single therapeutic strategy. Today, we still need to make use of the full range, variety, and combination of different therapeutic strategies, such as inpatient and outpatient treatment, the differential and sequential use of psychopharmacological compounds, pharmacological combination and augmentation strategies, as well as other highly effective biological treatments including light therapy, ECT and transcranial magnetic stimulation, and psychotherapy, in order to deal with this illness acutely, since clinicians are often reluctant to ask questions about a patient’s sexual life. In addition, these results do suggest that suicidality should be given notably more attention in patients with a fast onset of a depressive episode. The core and illness-defining symptoms that develop in the further course of depression are depressed mood and/or the inability to experience joy (anhedonia).

Different depressive syndromes can develop, depending on which symptoms evolve. From a psychopathological perspective, the most important ones that we differentiate today, because of their different prognostic and therapeutic implications, are melancholic, atypical, and psychotic depression. Recently, Gin Mahli and Gordon Parker developed a model for the relationship between psychotic melancholia, nonpsychotic melancholia, and nonmelancholic depression, and the major monoamines thought to be involved in depression. The authors postulate that in nonmelancholic depression with its primary affective symptoms, serotonergic dysfunction may prevail, while nonpsychotic melancholia, which is accompanied more by psychomotor disturbance, derives from a more pronounced norepinephrine dysfunction. With respect to psychotic depression, dopamine may be involved to a higher degree (Figure 2). As another example, the subtype of atypical depression can be mentioned here, which has long been seen as an indication for treatment with monoamine oxidase inhibitors.

Finally, in a full-blown depressive episode, depressive symptoms appear in the following percentages (data from 1014 depressed inpatients using the 21-item Hamilton Rating Scale for Depression [HAM-D21]; given in declining order of percentage): depressed mood 99.4%, loss of interest in work and activities 99.2%, somatic symptoms 85%, psychic anxiety 84.3%, feelings of guilt 78.5%, insomnia middle of night 78.3%, genital symptoms 76.6%, suicidal ideation 76.5%, insomnia early night 71.4%, somatic anxiety 71.2%, insomnia late night 66.8%, diurnal variation 66.5%, loss of appetite 64.4%, psychomotor retardation 55.6%, agitation 49%, loss of weight 48.6%, hypochondriasis 39%, depersonalization 30.9%, paranoid ideas 21.5%, lack of illness insight 18%, and compulsiveness 10.1%. The distinct pattern or cluster of symptoms that comes to the fore in an individual could lead the way toward finding a more individualized treatment regimen, which might speed up the time to response. For example, in patients with anxiety symptoms, a combination of an antidepressant with a benzodiazepine may lead to a quick reduction in the sensation of fear. Also, sleep disturbances can be addressed specifically with hypnotic comedication or a sedating antidepressant.
What symptoms are predictive of remission and what is the timing of their alleviation?

Despite the fact that response and remission are gaining more and more acceptance in the research community as major outcome criteria in clinical trials as a result of their important clinical implications compared with mean-score differences, most trials still rely solely on end point differences between drug and placebo for remission or response rates. Only a few report both rates, and even fewer also report the time course of response and remission rates.

Generally speaking, the course of remission and response under treatment seems to follow a typical pattern: the strongest effects in terms of a mean score reduction usually appear at the beginning of the antidepressant therapy regimen, not only in phase 3 studies sponsored by pharmaceutical companies but also in naturalistic studies. By far the most pronounced HAM-D mean score decline can thus be seen after the first 2 weeks of a newly initiated treatment. Thus responding to an antidepressant therapy might boost good functional recovery and lower relapse rates.

Achievement of remission is highly predictive of good functional recovery and lower relapse rates. Thus responding to an antidepressant therapy might represent advancement of the healing process in end to about 7%.28 Remission rates started at about 11% after week 2 and went up to about 22% at week 6 and declined again to 14% at study end. Interestingly, until week 4, there were higher response than remission rates, and from week 6 onward, the relationship was the opposite, with higher remission than response rates (Figure 3).18 With respect to the latter phenomenon, a strikingly similar picture is revealed by our own data on naturalistic-treated inpatients (Figure 4, page 122).17,18 At week 6, the remission rate surpasses the response rate up to the final visit. This clearly justifies and underlines the importance of differentiating and calculating both response and remission rates as two different outcome variables. These results further imply that response usually precedes remission, which is also strengthened by the notion that achievement of response is highly predictive of remission.

Achievement of remission is highly predictive of good functional recovery and lower relapse rates.
Timing of onset of antidepressant action

Traditionally, it has been thought that standard antidepressants take about 1 month for their action to fully unfold, and that they have a delayed onset of action of at least 2 weeks. Identification of the exact timing of the onset of antidepressant action has been a well-debated matter for the last 20 years. Originally, Frederic Quitkin proposed in his pattern analytic approach that real drug-placebo differences could not be observed before 3 weeks of treatment. An earlier improvement was associated with a placebo response and a lack of sustained improvement, whereas the opposite was true for true drug responders, who showed a delayed but sustained onset of improvement. More recently, this view has been questioned by a large number of authors, including Stassen and Szegedi, who have not only emphasized that an earlier onset of improvement before 2 weeks was highly prevalent, but also showed that it was highly predictive of later outcome. An early improvement was therefore defined as a 20% reduction in the initial HAM-D17 score within the first 2 weeks. Today, there is strong evidence that early onset of antidepressant action exists and appears to be highly sensitive for later response or remission. These results can best be translated into clinical practice as follows: if after 2 weeks no improvement at all can be observed under a new antidepressant regimen, then the pharmacologic regimen should be adjusted or changed early rather than waiting for another 2 or 3 weeks. In this case, if no alteration of the treatment has occurred, the chances of this person still responding are below 20%. However, there are a number of methodological pitfalls inherent in the study of this phenomenon. The rating scales currently in use such as HAM-D and MADRS were never developed to detect early changes in psychopathology due to antidepressant action. In addition, most publications on this topic rely on post-hoc analysis of phase 3 trials not designed for the detection of an early onset of action, with 2-week rating intervals not allowing the detection of earlier improvements. The inconsistencies in Quitkin’s conclusions can best be explained by methodological differences between the two approaches. Quitkin et al defined stable drug response very strictly as “much improvement” on the clinical global impression scale. As pointed out by Geilenberg, it might be that the lag in the onset of antidepressant action observed by Quitkin was caused by the high degree of improvement necessary for response. In other words, authors such as Stassen and Szegedi observed earlier effects, because they used lower and more sensitive cut-off values, which enabled them to detect minor changes earlier.

One of the few studies specifically designed to study the onset of action of antidepressants was conducted by Rojo and coworkers. They investigated the onset of antidepressant action in 582 depressed outpatients with HAM-D17 assessments at baseline and after 1, 2, and 4 weeks. Patients were treated with mirtazapine and, depending on the timing of response, sustained responders were subdivided into four groups: very fast responders, fast responders, traditional responders, and nonresponders. At baseline, only a few symptoms captured by HAM-D17 showed significant differences between the responder groups; ie, items such as guilt, suicide, and genital symptoms: the more severe these baseline variables were, the slower was the response.

Order and timing of symptom alleviation

The order and timing of the alleviation of depressive symptoms has also rarely been studied. With respect to the Rojo study, across all four subgroups, the pattern on a symptom level did not vary: first, all groups improved on items such as depressed mood, early insomnia, and psychic anxiety. Second was improvement on the HAM-D item “general somatic symptoms.” Interestingly, this improvement pattern occurred for the very fast group within the first week, for the fast group within the second week, and for the traditional group within the third week. In summary, the alleviation of HAM-D17 symptoms for each subtype was similar, but occurred at a different time in each responder group. These results suggest that this equal response may not depend on personality traits, doctor-patient relationships, or medical practice, but rather on pharmacological factors and pharmacokinetics, at least in the case of mirtazapine.
In our own naturalistic follow-up study on 1014 depressed inpatients, we observed the long-term alleviation of the 6 core items of HAM-D (Seemüller et al, unpublished data). Apart from item 1, all of the other 5 items 4,10,11,23,35 paralleled the same decline pattern until discharge, with the most pronounced difference between baseline and week 2. Item 1 of HAM-D, however, referred to as “depressive feelings,” showed the strongest and fastest decline of all items up to discharge (Figure 5).

In another large naturalistic trial on escitalopram in 11 760 outpatients, patients were asked to name the MADRS symptoms that changed the most 2 weeks after starting antidepressant therapy. Patients most frequently answered that “inner tension,” followed by “sadness,” “pessimistic thoughts,” and “reduced sleep” had changed as early as week 2.

Unfortunately, a substantial proportion of patients do not respond to treatment within this short time period, and most depressed patients do not initially achieve remission. In STAR*D, only 28% of the initial sample of 2876 depressed patients achieved remission, and 47% were responders with citalopram. The longer the search for an effective antidepressant treatment in an individual, the higher the potential risk of chronicity, the higher the overall costs, and the worse the functional outcome. If a patient could be detected and identified early on as being a nonresponder to an antidepressant and could consequently be referred earlier to a more effective strategy such as dual-acting antidepressants, augmentation strategies like lithium augmentation or augmentation with an atypical antipsychotic, or to other highly effective treatments such as ECT, the difficult challenge of optimizing the treatment of depression could be facilitated.

Clinical predictors of response to antidepressant medication

One way to classify predictors is to distinguish between biological and clinical predictors, meaning either predictors that can be measured with a distinct laboratory test or predictors that can simply be observed or asked about. In clinical research, in addition to the classification of subtypes of depression, clinical/anamnestic predictors have been examined regarding the response to antidepressants. The following have been relatively consistently described as being relevant to a rather poor response to antidepressants—most have been also confirmed in later examinations: poor social adaptation, neurotic traits in the premorbid personality, number and duration of earlier psychiatric inpatient treatments, nonresponse to earlier treatments with antidepressants, chronicity of the depressive symptoms, mild degree of depressive symptoms, delusions, and absence of vital symptoms.

However, the variance rates described by single predictors are for the most part so minor that they are hardly usable for practicable prognostics in individuals. In addition, there are hardly any hypothesis-free approaches investigating a whole set of different psychopathologic measures and clinical variables with respect to their prognostic meaning. So far, the predictors we know of can at best contribute to group statistical differentiation. Future research should also focus on the possibility of combining predictors, thereby potentially enabling prognosis to be optimized.

Why are available antidepressants not always able to achieve remission?

Partial response and nonresponse to antidepressant medications are a common problem in patients with depression. Between 10% and 30% of depressed patients taking an antidepressant are partially or totally resistant to the treatment. Recurrence of depression while still taking medication (ie, breakthrough) can also occur. In our own cohort of 1014 depressed inpatients, about 32% of all patients suffered from an index episode that lasted longer then 6 months and were therefore classified as partially refractory patients.

![Figure 5. Individual item changes for the 6 core symptoms on the 17-item Hamilton Rating Scale for Depression in naturalistic-treated depressed patients.](image)
In addition, comorbidities such as substance abuse, personality disorders, and general medical disorders including hypothyroidism and anemia can also influence the overall success of a treatment plan and can muddy the water. In particular, medical comorbidities might negatively influence outcome in two ways: first, through the direct impact of the medical comorbidity on the psychiatric illness, and second, through adverse effects of medications used to treat the medical comorbidities, also known as pharmacogenic depression. With regard to relapse rates after complete remission, Andrew Nierenberg demonstrated most recently in his talk at the Collegium Internationale Neuro-Psychopharmacologicum congress in Munich, showing data from STAR*D, that the higher the load for psychiatric comorbidities, the higher the risk of relapse over 1 year.44

The reasons for true drug resistance remain unknown. Unfortunately, even the definition of drug resistance is not fully standardized and varies greatly across different studies. In daily clinical practice, probably the most useful definition might be as follows: drug nonresponse to at least two adequate trials of antidepressants (adequate dosage and treatment duration) with different mechanisms of action. Given the aforementioned complexity and diversity of the etiopathogenesis of such a multifaceted illness like depression, a “one treatment fits all” approach to regaining a new homeostasis on a transmitter level and a functional level at the same time cannot be very fruitful.

New ideas regarding the underlying pharmacological mechanisms that cause a poor response may lead to a more personalized therapy that is based on “the right drug for the right patient.” One new way forward might arise from a recent study on the ABCB1 drug transporter gene, in which the basic idea was that every antidepressant drug must pass the blood brain barrier before its antidepressant activity can unfold. P-glycoprotein (P-gp),43 which is encoded on the ABCB1 gene, serves as a transporter and acts as an efflux pump for a wide range of pharmacological compounds. Uhr and colleagues were able to identify the antidepressant substrates of P-gp, and could predict response and remission in relation to the genotype of subjects who were treated with antidepressants that were substrates of P-gp.44 A completely different approach may arise from the use of brain imaging techniques. Frodl and coworkers, for example, were able to demonstrate that nonresponders to antidepressant treatment showed significantly lower amygdala volumes at baseline than did remitters.35

**Conclusion**

In summary, aside from the complexity of this inhomogeneous illness, several factors may contribute to treatment failure, including undiagnosed or misdiagnosed medical conditions such as hypothyroidism and anemia. The patient who does not respond or only partially responds to an antidepressant should therefore first be reassessed to make sure the original diagnosis of depression was correct. Also, nonpsychiatric drugs such as methylodopa, β-blockers, and reserpine can cause or exacerbate depression, and comorbid disorders (eg, eating disorders, substance abuse or dependence) may affect treatment response. Psychotic depression, melancholic depression, and atypical depression are depressive subtypes that may require concurrent pharmacotherapy such as antipsychotic or augmentative psychotherapy. Finally, adverse effects and poor compliance may be additional obstacles to successful treatment, but with our growing understanding of the pathophysiology of the illness, there is hope that in the near future we will be making progress in the direction of individualizing the clinical decision-making process.

**DÉLAI DE RÉPONSE ET RÉMISSION AU COURS DU TRAITEMENT ANTIDÉPRESSEUR**

L’onset de réponse et de rémission au cours du traitement antidépresseur est un des moments clés de la prise en charge des patients dépressifs. Il est donc intéressant de comprendre comment ces phénomènes se traduisent sur une échelle temporelle.

1. **Définitions**

   - **Dépression majeure** : maladie neurologique caractérisée par une douleur persistante et intense. Elle est souvent liée à des facteurs génétiques, environnementaux et psychosociaux.
   - **Rémission** : disparition des symptômes sévères d’une manière durable.
   - **Dépistage des symptômes** : utilisation de questionnaires spécifiques pour détecter les éléments de la dépression.

2. **Facteurs qui influencent la dépression**

   - **Biologiques** : perturbations neuroendocrines et neurotransmissives.
   - **Psychologiques** : facteurs de stress, catastrophisation, maladie de vie.
   - **Génétiques** : familiaux, monozygotic, dizygotic.

3. **Étapes de traitement**

   - **Délai de réponse** : temps nécessaire pour que l’effet thérapeutique se manifeste.
   - **Délai de remise** : temps nécessaire pour que les symptômes soient complètement résolus.

4. **Prédictions théoriques**

   - **Délai de réponse** : environ 1 à 2 semaines pour certains traitements.
   - **Délai de remise** : environ 4 à 8 semaines pour certains traitements.

5. **Études cliniques**

   - **Délai de réponse** : études cliniques montrent que le délai de réponse peut varier de 2 à 8 semaines.
   - **Délai de remise** : les études cliniques montrent que le délai de remise peut varier de 3 à 6 mois.

6. **Délai de réponse et remise**

   - **Délai de réponse** : pour les antidépresseurs tricycliques, il est de l’ordre de 2 à 3 semaines.
   - **Délai de remise** : pour les antidépresseurs biphényles, il est de l’ordre de 3 à 4 semaines.

7. **Facteurs qui influencent le délai de réponse et de remise**

   - **Densité de la dose** : plus la dose est élevée, plus le délai de réponse est court.
   - **Détectabilité des symptômes** : plus les symptômes sont détectables et plus le délai de remise est court.

8. **Études de suivi**

   - **Délai de réponse** : études de suivi sur plusieurs années montrent que le délai de réponse est d’environ 2 semaines pour les antidépresseurs tricycliques.
   - **Délai de remise** : études de suivi sur plusieurs années montrent que le délai de remise est d’environ 4 semaines pour les antidépresseurs tricycliques.

9. **Prédictions thérapeutiques**

   - **Délai de réponse** : prédire le délai de réponse peut aider à la gestion du traitement.
   - **Délai de remise** : prédire le délai de remise peut aider à la gestion des attentes des patients.

10. **Études sur la réponse et la remise**

    - **Délai de réponse** : études cliniques montrent que le délai de réponse est d’environ 2 semaines pour les antidépresseurs tricycliques.
    - **Délai de remise** : études cliniques montrent que le délai de remise est d’environ 4 semaines pour les antidépresseurs tricycliques.

**Remarques**

- Le délai de réponse et de remise est influencé par un grand nombre de facteurs, y compris les caractéristiques génétiques, les facteurs environnementaux, et les caractéristiques du patient.
- Les patients avec des antécédents de dépression ou des antécédents de maladies psychiques se démarquent généralement par un délai de réponse et de remise plus long.
- Les traitements de support et les traitements cognitivo-comportementaux peuvent également influencer le délai de réponse et de remise.

**Conclusion**

Le délai de réponse et de remise au cours du traitement antidépresseur est un phénomène complexe et multifactoriel qui nécessite une approche holistique et intégrée pour être compris et géré de manière appropriée.

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**Time course of response and remission during antidepressant treatment – Möller and others**

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The influence of comorbid anxiety disorders on outcome in major depressive disorder

by D. S. Baldwin and A. T. V. Lopes, United Kingdom

Anxiety symptoms are common in patients experiencing major depressive episodes, being reported by approximately 60% of patients, and comorbid anxiety disorders are seen in around 50% of patients with major depressive disorder. One of the early findings of the influential US Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study was that “anxious depression,” defined as a score of 7 or greater on the anxiety-somatization subscale of the Hamilton Rating Scale for Depression, was seen in 49% of the patients in primary care, and by 42% of those treated in secondary care. Furthermore, a comorbid anxiety disorder was present in approximately half of patients, regardless of the treatment setting. This degree of comorbidity is also seen in nonclinical samples: for example, the results of a systematic review of European community studies among people aged 18-65 years found that approximately 30%-40% of patients with a depressive disorder had a comorbid anxiety disorder, and vice versa. The recent European Study of the Epidemiology of Mental Disorders (ESEMeD) also found a high 12-month prevalence of comorbid mood and anxiety disorders (Figure 1).

There have been few studies of the comorbidity between anxiety and depressive disorders in later life, although a Dutch community study of people aged 55-85 years found that 47.5% of those with a major depressive disorder also met criteria for at least one anxiety disorder, and 26.1% of those with anxiety disorders fulfilled the criteria for major depression. This observation is supported by the findings of studies involving clinical samples of older depressed patients, in whom comorbid anxiety disorders have been found to vary in frequency from between 3%-65%.

Keywords: major depression; anxiety disorder; comorbid; outcome; response

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition Text Revision</td>
</tr>
<tr>
<td>ESEMeD</td>
<td>European Study of the Epidemiology of Mental Disorders</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>STAR*D</td>
<td>Sequenced Treatment Alternatives to Relieve Depression (study)</td>
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This review examines three key aspects of the relationship between major depressive disorder and comorbid anxiety disorders. First, whether the comorbid condition is more severe than “pure” major depression; second, whether the comorbid condition is associated with worse clinical outcomes than are seen in major depressive disorder alone; and third, whether the response to antidepressant treatment differs between depressed patients with or without comorbid anxiety disorders.

Greater severity of symptoms and impairment in the comorbid condition

Early studies supported the widespread consensus that patients with comorbid mood and anxiety disorders had more severe symptoms. Subsequent studies have in general supported this view. For example, a comparison of 276 US primary care depressed patients with or without a lifetime comorbid anxiety disorder demonstrated that the presence of comorbid panic disorder was associated with greater severity of depressive symptoms, more marked impairment in psychosocial functioning, and greater risk of prematurely stopping treatment.

Similar findings were seen in a more recent naturalistic study of the effects of coexisting anxiety symptoms or comorbid anxiety disorders on symptom severity at baseline and treatment response, in Italian outpatients with major depressive disorder. It was found that the presence of anxiety symptoms and disorders was associated with more frequent suicidal thoughts, greater psychomotor retardation, and greater severity of diurnal variation of symptoms, sexual dysfunction, somatic concerns, and weight loss, when compared with patients with major depressive disorder alone.

The greater symptom severity associated with the presence of comorbid anxiety disorders is also seen in other age groups: for example, a comparison of the effectiveness of interpersonal psychotherapy versus “treatment as usual” in depressed adolescents (aged 12-18 years) found that comorbidity was associated with both a greater severity of depressive symptoms at baseline, and with lower response rates in both treatment groups.

The greater symptom severity of the comorbid condition is reflected in a more pronounced degree of impairment of social and occupational functioning. For example, a recent large cross-sectional primary care study performed in Belgium and Luxembourg found that patients with comorbid major depressive disorder and generalized anxiety disorder reported greater impairment of work, and social and family life, than did patients with major depression or generalized anxiety disorder alone.

Epidemiological studies demonstrate that a number of individuals have multiple comorbid diagnoses, and some of the greater impairment that is associated with comorbid depressive and anxiety disorders may reflect the presence of additional mental health problems. For example, the presence of comorbidity for an anxiety disorder in patients with major depressive disorder has also been associated with greater risk of comorbidity for personality disorders: in the aforementioned comparison of US primary care depressed patients, lifetime comorbidity for panic disorder was also associated with the presence of avoidant personality disorder.

The adverse effects of anxiety disorder comorbidity in patients with unipolar depressive disorder are sometimes also seen in patients with the diagnosis of bipolar disorder, although not all studies have produced consistent findings. An investigation in a consecutive sample of French bipolar inpatients found that those with a lifetime comorbid anxiety disorder (24% of the overall sample) did not differ in terms of disorder severity (assessed by number of hospitalizations, presence of psychosis, substance misuse comorbidity, and suicide attempts), although their response to anticonvulsant drugs was lower than that of the group without comorbid anxiety disorders. By contrast, in a longitudinal study of the effects of comorbid anxiety disorders on bipolar disorder patients treated with psychotropic drugs, either alone or in combination with family intervention, comorbidity was associated with greater symptom severity at baseline (even after controlling for depressive symptom severity) and with poorer overall treatment response over 28 months, regardless of the treatment modality. The link between bipolar disorder and anxiety disorders is also emphasized by the findings of an investigation of the factors associated with non-response to antidepressant treatment in patients with apparent unipolar depression, which found that the presence of comorbid anxiety disorders was associated with a greater “risk” of unrecognized bipolar disorder:

Poorer outcome in longitudinal studies in patients with comorbid conditions

The presence of comorbid anxiety disorders with major depression is usually found to be associated with a less favorable long-term outcome. For exam-
ple, an early systematic review of the clinical outcome of anxiety and depressive disorders found that patients with comorbid anxiety and depression had generally worse outcomes than patients with either an anxiety disorder alone, or a depressive disorder alone.22

The findings of the United States National Comorbidity Survey indicate that participants were significantly more likely to continue presenting with symptoms of a major depressive if they also fulfilled criteria for comorbid generalized anxiety disorder. Similarly, patients with generalized anxiety disorder and comorbid major depression were more likely to experience continued anxiety symptoms than those without depressive symptoms (Figure 2).21

The adverse effects of coexisting anxiety symptoms in depressed patients is generally thought to be associated with higher treatment drop-out rates, a delayed recovery in patients with comorbid generalized anxiety disorder, and particularly poor response in depressed patients with lifetime panic disorder.33

The adverse effects of comorbidity are also manifested through a greater risk of recurrence of symptoms and possibly through an increased risk of suicide. By way of illustration, long-term follow-up (up to 5 years) of a Finnish nationally representative sample of outpatients with DSM-IV (Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition)–defined major depressive disorder found that the severity of symptoms and the presence of comorbidity, especially for social phobia, predicted both a higher probability of recurrence and a greater number of recurrences.29

While the increased risk of suicide in depression has been known for many years, it remained uncertain as to whether anxiety disorders were also associated with an elevated risk of suicide. However, in recent years, epidemiological studies and a systematic review have demonstrated that anxiety disorders are associated with suicidal thoughts and with attempted, if not completed, suicide.26,30 Moreover, current data indicate that comorbid anxiety disorders amplify the risk of suicide attempts in people with mood disorders.30 As the two greatest risk factors for completed suicide are suicidal thoughts and a recent suicide attempt, it therefore seems reasonable to assume that anxiety disorders carry an increased risk for completed suicide.

Reduced response rates and less remission of symptoms during treatment

The presence of prominent anxiety symptoms in depressed patients is generally thought to be associated with a lower overall response rate to treatment. For example, an early comparison of the effectiveness of interpersonal psychotherapy or treatment with the tricyclic antidepressant nortriptyline in 157 depressed patients in primary care found that lifetime comorbidity for an anxiety disorder was associated with higher treatment drop-out rates, a delayed recovery in patients with comorbid generalized anxiety disorder, and particularly poor response rates in patients with lifetime panic disorder.33

Subsequently, a comparison of small groups of patients with major depressive disorder that did or did not respond to antidepressant treatment found that comorbid anxiety disorders (and reports of childhood emotional abuse) were significantly more frequent among the nonresponders.30 A much larger randomized trial of stepped collaborative care of 228 depressed patients in a US health maintenance organization found that the presence of comorbid panic disorder was associated with both greater symptom severity at baseline, and with a significantly lower treatment response.35

Furthermore, in a recent investigation of the determinants of non-response in patients with treatment-resistant depression, a comorbid anxiety disorder was the clinical factor most strongly associated with non-response.26
The adverse effects of comorbidity on the response to treatment are seen in a variety of age groups. For example, an evaluation of the effectiveness of cognitive behavioral therapy, systemic behavioral therapy, and nondirective supportive therapy in 101 adolescents (aged 13 to 18 years) fulfilling DSM-III-R criteria for major depression found that the presence of anxiety disorder comorbidity was predictive of symptom persistence. At the other end of the age distribution, a longitudinal study in older adults undergoing case management, cognitive behavior therapy, or the combination for treatment of depression found that comorbid anxiety disorders were associated with greater symptom severity at the end of treatment and at follow-up at 6 and 12 months.

However, not all the evidence for the effect of coexisting anxiety symptoms or comorbid disorders on treatment response is consistent. For example, a comparison of small groups of Australian inpatients with DSM-III-R-defined major depression found that the presence of comorbid anxiety disorders did not affect either treatment choice, or the effectiveness of treatment interventions. In addition, a greater severity of coexisting anxiety symptoms at baseline among patients with either chronic major depression or “double depression” (that is, dysthymia plus supervening acute major depression) did not affect overall response rates with either the tricyclic imipramine or the selective serotonin reuptake inhibitor (SSRI) sertraline. Furthermore, in both a comparison of the effectiveness of the tricyclic nortriptyline and the SSRI paroxetine in 116 depressed patients aged 60 years or older, and a second comparison of the effectiveness of paroxetine or interpersonal psychotherapy in 125 patients aged 69 years or older, no difference was found in the proportion responding to treatment or in the time to response, between patients with or without anxiety.

Although outside the scope of this review, it is worth noting that the adverse effects of comorbidity are also seen among patients with primary anxiety disorders. For example, a recent evaluation of clinical outcomes at 1 year following cognitive behavioral therapy in outpatients with panic disorder, with or without agoraphobia, found that the presence of comorbid mood disorders was associated with lower response rates and a reduction in the proportion entering symptomatic remission.

Comorbidity of major depressive disorder with anxiety disorders has also been associated with a reduced likelihood of achieving symptomatic remission with antidepressant treatments. The findings of STAR*D, sequential treatment of 2876 depressed patients, found that the presence of a comorbid anxiety disorder at baseline was associated with significantly lower rates of achieving symptomatic remission during the initial intervention (with the SSRI, citalopram). However, as with studies of overall treatment response, not all evidence is consistent: for example, an evaluation of the effects of comorbid anxiety disorders on response to treatment with the SSRI fluoxetine in 329 patients with DSM-IV-defined major depressive disorder, found no major adverse effects of comorbidity on the likelihood of achieving symptomatic remission.

Lower response rates and reduced likelihood of achieving symptom remission are factors that may lead to a greater perceived need to utilize antidepressant drugs, and to the concomitant use of two or more antidepressant or other psychotropic drugs, in an attempt to improve outcomes. Data from the recent Canadian Community Health Survey on Mental Health and Well-Being show that the comorbidity of major depressive disorder with anxiety disorders is associated with somewhat higher rates of use of antidepressant drugs than that seen for major depressive disorder alone.

The need for studies in patients with comorbid mood and anxiety disorders

The presence of comorbid depressive disorders is usually regarded as an exclusion criterion in randomized placebo-controlled trials of antidepressants in patients with primary anxiety disorders, where proof of efficacy requires the demonstration that anxiety symptoms do not resolve indirectly, meditated by an effect on depression. In addition, depressed patients with comorbid anxiety disorders are often excluded from participating in studies with new antidepressant treatments, perhaps because the presence of significant anxiety symptoms may reduce response rates, and thereby impede the chance to distinguish antidepressant from placebo effects. However, comorbidity is the rule in clinical practice, and it is helpful to know whether a single medication can diminish the severity of both anxiety and depressive symptoms in patients with comorbid conditions. However, there are relatively few studies that have specifically focused on investigation of the treatment response in comorbid patients.

An investigation of the effectiveness of open treatment with the SSRI fluoxetine (20 mg/day) in 123 US outpatients with major depressive disorder and at least one comorbid anxiety disorder, both defined according to DSM-III-R criteria, found that it reduced depressive symptom severity between baseline and study end point: however, patients with depression and comorbid obsessive-compulsive disorder were significantly less likely to respond to treatment than patients with other comorbid anxiety disorders. A subsequent open but controlled comparison of paroxetine (20-40 mg/day) with moclobemide (a reversible inhibitor of monoamine oxidase A) at a dosage of 300-600 mg/day in 123 Italian outpatients with DSM-III-R-defined major depressive disorder or dysthymia and comorbidity anxiety disorder found no significant difference in overall response between the two antidepressants: however paroxetine was superior to moclobemide in the subgroup of 32 patients with comorbid panic disorder.

The open design and lack of placebo control in these investigations together prevent definitive conclusions being drawn about the potential efficacy of certain antidepressant treatments in comorbid patients. A randomized double-blind comparator-controlled trial of sertraline (50-100 mg/day) and imipramine (100-200 mg/day) in patients with comorbid major depressive disorder and panic disor-
under found no differences between treatments in the reduction of depressive and panic symptom severity, treatment outcome being concordant for both diagnoses in approximately 70% of patients. Again, the absence of a placebo control hinders definitive conclusions, and there is a persistent need for large multicenter studies in patients with comorbid mood and anxiety disorders, that employ a placebo-controlled design.

Conclusions

Anxiety symptoms are integral to major depressive episodes, and many patients with major depressive disorder will have prominent anxiety symptoms: furthermore, a significant proportion of depressed patients will show either lifelong or concurrent comorbidity for anxiety disorders. In general terms, the presence of comorbid anxiety disorders is associated with a greater severity of symptoms and more pronounced symptom-related disability and impairment, with a less favorable outcome, greater risk of symptom persistence, recurrence, and possibly suicide, and a less satisfactory response to antidepressant treatment. It is also associated with lower rates of recovery and a reduced likelihood of achieving symptomatic remission. There is a clear need for further randomized controlled trials in patients with comorbid mood and anxiety disorders, as this group comprises a probable majority of depressed individuals seen within routine clinical practice settings.

REFERENCES


**Impact des troubles anxieux comorbides sur la rémission de la dépression**

La coexistence de symptômes anxieux et de troubles anxieux comorbides est fréquente chez les patients atteints de troubles dépressifs majeurs (TDM). Cet article étudie trois aspects de la relation entre les TDM et les troubles anxieux comorbides : lorsque l’état comorbide est plus sévère que la dépression majeure « pure » ; lorsque l’évolution clinique de l’état comorbide est plus sévère que celle des TDM isolés ; et lorsque la réponse au traitement antidépresseur diffère entre les patients avec ou sans troubles anxieux comorbides associés. En général, même si les données ne sont pas toutes concordantes, la présence de troubles anxieux comorbides chez les patients atteints de TDM est associée à une plus grande sévérité des symptômes et à une atteinte plus prononcée. L’évolution de la maladie est moins favorable chez les patients atteints de comorbidity et un plus petit nombre d’entre eux répondent au traitement antidépresseur et obtiennent une rémission de leurs symptômes. Des études randomisées contrôlées contre placebo sont nécessaires chez les patients souffrant de TDM et de troubles anxieux comorbides afin de déterminer si ces derniers diffèrent de ceux souffrant de dépression majeure « pure » dans la réponse aux traitements pharmacologiques et psychologiques.
Over the course of evolution, organisms have developed cellular clock mechanisms sensitive to light, and have adapted by organizing their activities in 24-hour cycles determined by sunrise and sunset. These cycles do not simply reflect an organism’s passive response to environmental changes, such as the light-dark cycle, but rather represent pre-adapted endogenous rhythms, which arise from a timekeeping system within the organism and that persist in the absence of any environmental stimuli. The endogenous timekeeping system or biological clock allows the organism to anticipate and prepare for the changes in the environment that are associated with day and night in order to function optimally.

Mood disorders, especially unipolar depression and seasonal affective disorder, have been linked to endogenous circadian rhythm abnormalities. Evidence is emerging that disruption of the normal circadian rhythmicity occurs at least in a subgroup of depressed patients, although whether there is a causal link between endogenous circadian rhythm disruption and depression has not been firmly demonstrated. Nonetheless, improvements in some forms of depression in response to strategies that manipulate circadian rhythms support the idea that circadian abnormalities observed in depressed patients may constitute a core component of the pathophysiology of depression and are worthy of therapeutic consideration. Chronotherapeutic interventions, which include both nonpharmacological strategies, such as sleep deprivation, light therapy, and interpersonal and social rhythm therapy, and pharmacological treatments based on the use of drugs specifically endowed with chronobiotic properties, such as agomelatine, have been shown to have antidepressant effects. Therefore, normalization of circadian rhythms seems to represent a possible new direction for the development of either pharmacological or nonpharmacological innovative therapeutic strategies, which could have an important future role as alternatives or adjuvants to currently available antidepressant treatments, in order to achieve a better quality of remission and a persistent amelioration of patients’ social functioning and quality of life.

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Keywords: circadian rhythm; depression; remission; chronotherapy; antidepressant

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Some patients with mood disorders suffer from regular cycles of altered mood.\(^1\) The mean plasma concentrations of thyroid stimulating hormone during Data with a novel antidepressant drug, agomelatine, point to a restoration of Polymorphic variants of clock genes have been found to be associated with Approximately 20% of depressed patients have marked diurnal variation in Diurnal mood variations in major depressive patients are paralleled by diur- Interpersonal and social rhythm therapy has shown preliminary effects in the Some patients with major depression show a lower blood concentration of A phase advance of the circadian motor activity rhythm has been detected in A certain number of depressed patients exhibit elevated nocturnal body temper- The mean plasma concentrations of thyroid stimulating hormone during sleep, its nocturnal peak, and the amplitude of its circadian rhythm have been reported to be lower in depressed subjects, with a phase advance of the nocturnal peak\(^7\) Individuals with depression, especially those with the melancholic subtype, show an overall increased cortisol secretion with a phase advance of the corti- Some patients with major depression show a lower blood concentration of melatonin and a phase advance, or trend toward a phase advance, of the mela- tonin circadian rhythm\(^10,12\) It has been demonstrated that in bipolar patients and their offspring, the sensitivity of melatonin to the suppressant effect of light is modified\(^11,12\) Most individuals with depression make subjective complaints about sleep- wake cycle alterations; they also show sleep architecture abnormalities\(^21-26\) A phase advance of the circadian motor activity rhythm has been detected in bipolar disorder patients during both the depressive and manic phases, as well as during euthymia\(^27,29\) Patients with seasonal affective disorder regularly suffer major depressive episodes that occur in the fall/winter Polypharmcic variants of clock genes have been found to be associated with mood disorders, especially bipolar disorder\(^30,38\) Sleep deprivation and light therapy have proven antidepressant effects\(^38,45\) Interpersonal and social rhythm therapy has shown preliminary effects in the prevention of mood episodes in bipolar patients\(^46,47\) Data with a novel antidepressant drug, agomelatine, point to a restoration of disrupted circadian rhythms in both animals and humans\(^49-53\) Some patients with mood disorders suffer from regular cycles of altered mood recurrence Approximately 20% of depressed patients have marked diurnal variation in mood, and a pattern of worse mood in the morning is incorporated into the formal DSM-IV criteria for the melancholic subtype of major depression Diurnal mood variations in major depressive patients are paralleled by diurnal variations in regional brain glucose metabolism\(^12\) A certain number of depressed patients exhibit elevated nocturnal body temperature, with a phase advance in the overall 24-hour pattern\(^13-16\) The mean plasma concentrations of thyroid stimulating hormone during sleep, its nocturnal peak, and the amplitude of its circadian rhythm have been reported to be lower in depressed subjects, with a phase advance of the nocturnal peak\(^7\) Individuals with depression, especially those with the melancholic subtype, show an overall increased cortisol secretion with a phase advance of the corti- Some patients with major depression show a lower blood concentration of melatonin and a phase advance, or trend toward a phase advance, of the mela- \(^1\) It has been demonstrated that in bipolar patients and their offspring, the sensitivity of melatonin to the suppressant effect of light is modified\(^11,12\) Most individuals with depression make subjective complaints about sleep- wake cycle alterations; 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In a recent post-hoc analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, it was reported that 21.6% of the depressed patients enrolled in the study experienced diurnal mood variation, and that compared with patients without diurnal mood variation, they exhibited more severe depression and were more likely to meet the criteria for the melancholic subtype of depression.\(^54\) Of note, a pattern of worse mood in the morning is incorporated into the for-
using a two-factor model of mood categorized according to positive affect and negative affect, diurnal variations in these two mood dimensions were compared between a group of patients with major depression and a group of healthy controls. Results indicated that depressed patients showed lower overall levels of positive affect, which increased over the course of the day as in healthy controls but with a backward-shifted acrophase, and higher overall negative affect levels, with maximum values occurring in the late morning and then decreasing over the rest of the day. Furthermore, Germain et al provided preliminary evidence that diurnal mood variations in major depressive disorder patients were paralleled by diurnal variations in regional brain glucose metabolism.

**Core body temperature**

For core body temperature, a robust circadian rhythm has been well established, with the highest values occurring in the evening and the nadir occurring during the last third of the night. An elevated nocturnal body temperature is the most consistently observed circadian abnormality in depression, and this aberration generally normalizes with clinical improvement. Although not confirmed by all studies, a phase-advance in the overall 24-hour pattern of body temperature has been also reported in many depressed patients. Moreover, in subjects experiencing a depressive episode, nighttime changes in body temperature have been found to be inversely correlated with nighttime changes in plasma levels of thyroid stimulating hormone (TSH). The mean plasma concentration of TSH during sleep, its nocturnal peak concentration, and the amplitude of its circadian rhythm have been reported to be lower in depressed subjects compared with both normal controls and remitted patients. Finally, the time of the nocturnal TSH peak has been found to be advanced during a depressive episode.

**Cortisol secretion**

In healthy subjects, maximal secretion of cortisol occurs in the morning; thereafter, there is a progressive decline over the day until the nadir is reached in the evening, immediately after falling asleep. Dysregulation of the HPA axis is extremely frequent in depressed patients. A meta-analysis on cortisol in depression revealed an overall increase in cortisol secretion, with the largest effect at the nadir of the circadian rhythm and an earlier onset of the first cortisol secretory episode, consistent with a phase-advance of the cortisol circadian rhythm in depression.

**Melatonin secretion and the sleep-wake cycle**

Several studies have also reported on alterations in the melatonin secretory pattern in depression: the most consistent finding has been a lower blood concentration of melatonin and a phase advance, or a trend toward a phase advance, of the melatonin circadian rhythm in individuals suffering from major depression; this was, however, not confirmed in all studies. Moreover, a modified sensitivity of melatonin to the suppressant effect of light has been demonstrated in bipolar patients and their offspring.

The sleep-wake cycle is the most obvious circadian rhythm in humans, and sleep disturbances represent a prominent feature of depression. Epidemiological studies estimate that 50% to 90% of patients with diagnosed depression complain about impairment of their sleep quality. Typically, the complaints of depressed patients are about the difficulty in falling asleep, frequent nocturnal awakening, and early morning awakening. Insomnia is thereby not only experienced subjectively, but also reflected objectively in altered sleep architecture, as first demonstrated by Kupfer and colleagues in the early 1970s. These abnormalities consist of impaired sleep continuity and duration, a reduction of slow-wave sleep (SWS), a shortening latency of the initial rapid eye movement (REM) phase, an increase in the proportion of REM sleep in the early part of the night, a prolongation of the first REM period, an increased amount of total REM sleep, and an increased number of eye movements during REM periods (REM density). Longitudinal electroencephalogram studies in depressed patients have described a tendency for REM sleep abnormalities to resolve with improvement of the depression, and even total normalization has been reported after successful treatment. However, other studies have reported the persistence of REM sleep and SWS abnormalities during remission, even after pharmacological treatments. Persistent and/or residual sleep disturbance has thereby been associated with an increased risk of relapse, and the persistence of reduced SWS has similarly been associated with more rapid and more frequent recurrence of depression.

**Motor activity**

Motor activity shows a typical circadian rhythm in humans, and most although not all investigations have documented a phase advance (early daily peak) of the circadian motor activity rhythm in bipolar disorder patients in both the depressive and the manic phases as well as during euthymia.

**Seasonal affective disorder**

Seasonal changes in mood, appetite, sleep, and daily living function occur physiologically in many individuals. If these variations are of sufficient severity to meet the criteria for a major depressive episode, occur regularly during fall/winter, and are generally followed by a remission during the subsequent spring and summer period, they may be regarded as an episode of seasonal affective disorder (SAD). SAD is a disorder with a circannual period, and patients with SAD present with apparent chronobiological abnormalities; hence, it is currently assumed that SAD is a disorder of seasonal biological rhythms. Abnormalities of circadian rhythms in SAD patients include sleep disturbances, quantitative changes and phase delays in cortisol and melatonin secretion patterns, and increases in the minima of the nocturnal body temperature as well as a phase delay of its 24-hour rhythm.
Disrupted circadian rhythms and the pathogenesis of major depression

The fact that a wide variety of endogenous rhythms are disrupted in individuals with depression has led to speculation that such disturbances are not unique to specific rhythms, but are associated, instead, with a disruption in the activity of the circadian master pacemaker in the SCN. Therefore, it is plausible that alterations of the molecular components of the endogenous clock system play a role in the disturbed circadian rhythms of mood disorder patients. The cellular machinery behind the circadian timing within the SCN neurons has been largely identified, and it is believed to be under genetic control. Genes encoding essential elements of the clock include, in mammals, period (per1, per2, per3), neuronal PAS domain protein-2 (NPAS2), circadian locomotor output cycles kaput (CLOCK), cryptochrome (Cry1, Cry2), and brain and muscle ARNT-like-1 (bmal1) genes. The proteins encoded by these genes are part of a circadian autoregulatory loop incorporating activators and suppressors of genes, whose activity thereby oscillates with a circadian period, thus generating the endogenous rhythmicity of SCN neurons.

Both animal and human studies have provided preliminary evidence of a role for circadian genes in mood disorders. Mice carrying a mutation in the CLOCK gene display a behavioral profile that is strikingly similar to human mania, including hyperactivity, decreased sleep, reduced depression-like behavior, lower anxiety, and an increase in the reward value for cocaine, sucrose, and medial forebrain bundle stimulation. Interestingly, many of those mania-like behaviors are reverted by chronic lithium administration and are rescued by expressing a functional CLOCK protein specifically in the ventral tegmental area of CLOCK mutant mice.

Studies in humans have begun to identify polymorphisms in certain circadian genes that are associated with mood disorders and, in particular, bipolar disorder. The T3111C single nucleotide polymorphism (SNP) of the CLOCK gene has been investigated in both major depression and bipolar disorder. Whereas no differences were found in allelic frequencies between individuals with a history of major depression and healthy controls, the CC genotype has been associated with a greater severity of insomnia during antidepressant treatment, a higher recurrence rate of bipolar episodes, and a reduced need for sleep in bipolar patients. In a family-based sample of bipolar patients, an analysis of 46 SNPs in 8 clock genes revealed a significant although modest association of BMAL1 and TIM genes with the mood disorder. An independent study using haplotype analysis confirmed the association of bipolar disorder with the BMAL1 gene and detected a new association with the PER2 gene. Finally, bipolar patients with the TT genotype of the T50C SNP of the glycogen synthase kinase-3β gene, which encodes an enzymatic protein regulating central clock mechanisms, were found to be of an earlier age at the onset of bipolar disorder and to experience less improvement from lithium therapy than patients with the TC or CC genotypes. Recent studies suggest that SNPs of PER2, NPAS2, and BMAL1 genes are associated with an increased risk for SAD; furthermore, certain allelic combinations of SNPs of these three genes have an additive effect, increasing the risk of developing SAD by 4.43 over other genotypes, and 10.67 over the most protective genotype.

Based on the above findings, it could be suggested that primary or secondary alterations of the biological clock at the molecular level could lead to disruptions in endogenous circadian rhythms, which in turn may generate the depressed state. Alternatively, it has been proposed that instead of or in addition to molecular abnormalities of the endogenous pacemaker, disturbances in environmental zeitgebers may cause depressive symptoms in biologically predisposed individuals. This social zeitgeber theory specifically postulates that depressive episodes arise as a consequence of life events causing a disturbance of social zeitgebers (ie, social factors such as the timing of meals, work schedules, social demands, personal relationships), which, in turn, derail an individual’s social rhythms. These disruptions can place substantial stress on the body’s capacity to maintain stable biological rhythms, particularly sleep-wake, energy, alertness, and appetite rhythms. Whereas in most individuals such rhythms will restabilize shortly after the destabilizing events, in predisposed subjects, they may precipitate a major depressive episode.

Finally, as suggested by Turek, the expression of most rhythms at the behavioral, physiological, and biochemical level is regulated by the integration of inputs from the circadian clock and the sleep-wake state of the organism. Thus, the circadian and sleep control centers have evolved together to ensure a timely coordination between the internal and external environment in order to optimize the survival of the species. Therefore, it could be that a primary circadian disturbance of the sleep-wake cycle leads to insomnia that may desynchronize many endogenous rhythms, which then, in turn, may lead to a depressed state. In support of this latter view, evidence has been provided that insomnia is a risk factor for the development of depression, as well as for relapse and recurrence. Most of the circadian abnormalities observed in the depressed state normalize with recovery, therefore it cannot be excluded that they arise as consequence of depression and do not represent the primary determinants of the affective disorder. However, even if so, the presence of disrupted endogenous rhythms might potentially contribute to the maintenance of depressive symptoms and might affect the course and/or the prognosis of the affective episode. Therefore, circadian abnormalities of depressed patients are worthy of clinical and therapeutic consideration.

Disrupted circadian rhythms and the treatment of depression

The ideal antidepressant treatment should combine high short-term efficacy for the acute phase of treatment with long-term efficacy and tolerability for...
the maintenance phase. This would result in a high quality of remission, in which patients are asymptomatic with no or only minimal residual symptoms, and experience a full restoration of day-to-day functioning and quality of life. Currently used antidepressant drugs, which act more or less specifically on brain monoamines, are frequently associated with significant limitations such as low remission rates, high risk of relapse, slow onset of response, discontinuation symptoms, and side effects—especially sleep disturbances. Since a disruption of the normal circadian rhythmicity occurs at least in a subgroup of depressed patients and is believed to play a role in the pathophysiology of depression, it is theoretically likely that interventions able to induce phase shift within the circadian system, so that normal rhythmic patterns are restored, may result in a high quality of remission. Therefore, chronotherapeutic interventions have been developed, and these include both nonpharmacological strategies, such as sleep deprivation, light therapy, and interpersonal and social rhythm therapy (IPSRT), and pharmacological treatments based on the use of drugs specifically endowed with chronobiotic properties.

**Sleep deprivation**

One night of total sleep deprivation induces rapid and effective, although short-lasting, antidepressant effects. Variants of total sleep deprivation, such as selective REM sleep deprivation and partial sleep deprivation, especially in the second half of the night, are also effective, although total sleep deprivation seems to be superior. However, the therapeutic effect of sleep deprivation does not last longer than one or maximally a few days, and this intervention seems to work in less than 50% of patients.

**Light therapy**

Light therapy is the treatment of choice for SAD, where its astonishing success has led to the conclusion that it has to be considered the most successful clinical application of the circadian rhythm concept in psychiatry. It moves from the hypothesis that reduced ambient light during fall/winter leads to SAD symptoms in predisposed individuals; thus lengthening the photoperiod by exposing patients to bright light early in the morning before dawn or in the evening has been proven to exert antidepressant effects. It has subsequently been proposed that most patients with SAD become depressed in fall/winter at least in part because the later dawn in winter causes a delay in the patients’ endogenous circadian rhythms with respect to clock time and the sleep-wake cycle. Therefore, providing a corrective phase advance should be useful in realigning endogenous rhythms with the sleep-wake cycle. In SAD patients, exposure to bright light in the morning, which causes a phase advance of endogenous circadian rhythms, has been shown to produce higher antidepressant effects than exposure in the evening, which causes a phase-delay of endogenous rhythms. However, some SAD patients are actually phase-advanced, and this may explain why in some studies, bright light scheduled in the evening has been proven to have an antidepressant effect that is equal to that of morning exposure.

**Guidelines for the treatment of SAD patients with bright light have recently been provided.** Standard light treatment involves exposure to 1 to 2 hours of a 2500–10000 lux light box in the morning immediately upon awakening, and for those patients who do not respond to this schedule, a trial of evening bright light (7–9 pm) may be necessary.

**Interpersonal and social rhythm therapy**

IPSRT was specifically designed to maintain regular daily rhythms, as well as identify and manage potential precipitants of rhythm disruptions, in accordance with the social zeitgeber theory that depressive episodes arise as a consequence of life events that disturb social zeitgebers. Therefore, restoring the depressed patient’s social zeitgebers, such as personal relationships, meals, exercise, and social demands, would result in normalization of biological rhythms and an improvement in mood. Two preliminary studies have shown that although increasing bipolar individuals’ social rhythm regularity did not improve their mood, participants treated with IPSRT experienced longer episode-free periods and were more likely to remain well in the 2-year preventive maintenance study phase.

**Agomelatine**

As for pharmacologic interventions, melatonin has been identified as having chronobiotic properties in both rodents and humans; therefore, it is supposed that the pineal hormone has an antidepressant effect. However, the few studies in which melatonin has been administered to depressed patients have found an improvement in sleep, but no effect on depressive symptoms and no enhancing effect on existing antidepressant therapies in patients with treatment-resistant depression. By contrast, agomelatine, a compound with agonistic properties at melatonergic MT₁ and MT₂ receptors and antagonistic properties at 5-HT₂C receptors, which are highly expressed in the SCN, has shown antidepressant properties in both preclinical and clinical studies. It must be pointed out that the antidepressant effect of agomelatine is not solely mediated via its melatonergic action at the MT₁ and MT₂ receptors, but rather also depends on the compound’s 5-HT₂C antagonistic property. This may explain the above reported lack of antidepressant action of exogenous melatonin, which acts only on MT₁ and MT₂ receptors. It seems that, differently from currently available antidepressant drugs, agomelatine possesses specific chronobiotic properties, since it was able to regulate the sleep-wake cycle and restore abnormal circadian rhythms in animal models of disrupted circadian rhythms. In patients suffering from major depression, a recent polysomnographic study indicated that agomelatine increased the duration of SWS and normalized its distribution throughout the night. In a head-to-head comparison study between venlafaxine and agomelatine in major depressive disorder patients, an earlier and better improvement of subjective
measures of getting to sleep, quality of sleep, and ease of awakening have been reported with agomelatine. Moreover, agomelatine has been shown to be significantly superior to placebo in rates of clinical response and remission in a study in which the remission criteria (Hamilton Rating Scale for Depression score $\geq 6$) were more stringent than usual; the comparator in this study, paroxetine, had lower response and remission rates. Finally, in all the above clinical trials, agomelatine exhibited a favorable sexual side-effect profile and was in general well tolerated. All these data are indicative of agomelatine's potential to normalize circadian rhythms, including sleep-wake cycle alterations, without sedative effects and no sexual impairment, which could possibly lead to better adherence to antidepressant treatment, optimization of the achievement of full recovery with a high quality remission, and restoration of patients' quality of life.

**Conclusion**

Although a number of effective antidepressant drugs have been introduced in recent years, there remain significant unmet needs in the treatment of depression. Only approximately 30% of depressed patients achieve remission, and even for remitted patients, residual symptoms or drug side effects (eg, sleep disturbances, sexual dysfunction, weight gain) can reduce the quality of remission. Moreover, some antidepressant side effects can impair short-term and long-term patient adherence to treatment, thus favoring no response, relapse, and/or recurrence.

At present, it is clear at the descriptive level that some individuals with depression have circadian rhythm abnormalities; whether there is, however, a causal link between endogenous rhythm disruption and depression has not been firmly demonstrated, although evidence seems to be emerging that this is the case. Nonetheless, improvement in some forms of depression in response to strategies that manipulate circadian rhythms support the idea that circadian abnormalities observed in depressed patients may constitute a core component of the pathophysiology of depression. Therefore, normalization of circadian rhythms seems to represent a possible new direction for the development of either pharmacological or nonpharmacological innovative therapeutic strategies to treat depression. This new direction, in which circadian rhythms are directly targeted, could hold promise for the identification of chronotherapeutic strategies that, compared with currently-available antidepressant treatments, could have more solid efficacy and fewer side effects, achieving a better quality of remission and a persistent amelioration of patients' social functioning with a more complete restoration of their quality of life.

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Circadian rhythm disturbances in depression: remission quality/treatment implications – The Ultimate Goal


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TROUBLES DU RYTHME CIRCADIEN DANS LA DÉPRESSION : CONSEQUENCES POUR LE TRAITEMENT ET LA QUALITÉ DE LA RÉMISSION

Les troubles de l’humeur, et en particulier les troubles dépressifs unipolaires et les troubles affectifs saisonniers, sont liés à des anomalies endogènes du rythme circadien. La perturbation de la rythmicité circadienne normale interviendrait au moins dans un certain sous-groupe de patients déprimés, le lien causal entre la perturbation du rythme circadien endogène et la dépression n’ayant néanmoins pas été formellement démontré. Cependant, l’amélioration de certaines formes de dépression en réponse à des stratégies agissant sur les rythmes circadiens permet de penser que les anomalies circadiennes observées chez les patients déprimés pourraient constituer une composante clé de la physiopathologie de la dépression méritant d’être prise en considération. Des actions chronothérapeutiques, comprenant à la fois des stratégies non pharmacologiques, telles que la privation de sommeil, la luminothérapie et la psychothérapie interpersonnelle et des rythmes sociaux (PTIRS), ainsi que des traitements pharmacologiques fondés sur l’utilisation de médicaments dotés de propriétés chronobiotiques, comme l’agomélatine, ont montré des effets ant dépressifs efficaces. Ainsi, la normalisation des rythmes circadiens représente une nouvelle direction possible pour le développement de stratégies thérapeutiques innovantes, pharmacologiques ou non, qui pourraient avoir un rôle futur important comme alternative ou adjuvant aux traitements antidépresseurs actuellement disponibles, afin d’obtenir une meilleure qualité de rémission et une amélioration durable de la qualité de vie et de fonctionnement social des patients.
Improvement of the sleep-wake cycle as a target for remission in depression

by C. R. Soldatos and C. G. Theleritis, Greece

Sleep in depression

It has long been reported that sleep is disturbed in depression.1-5 Epidemiological studies have demonstrated that 50% to 90% of patients suffering from depression complain of poor sleep.6 In a large European community study, for instance, 63% of patients diagnosed with depression reported sleep problems.7 On the other hand, it has been reported that about 20% of subjects with insomnia screened in general population studies are found to be depressed.8-10 Moreover, subjective reports of sleep disturbance and objectively assessed polysomnographic abnormalities have been correlated with an increased risk of new-onset major depression,11 persistence of depressive symptomatology,12 and recurrence of depression following successful treatment.13 Polysomnographic studies have documented several sleep disturbances in depression: difficulty in initiating and maintaining sleep, prolonged sleep onset latency, multiple awakenings during the night, early morning awakening, and decreased total sleep time.1,3,5,6 Furthermore, slow-wave sleep (SWS) and rapid eye movement (REM) sleep are often found to differ between depressed patients and healthy individuals.1,14 Abnormal sleep architecture in depressed patients is reflected in reduced SWS,15 a greater number of stage shifts, earlier onset and a higher percentage of REM sleep, especially in the early part of the night, and an increased REM density.16

Sleep disorders have been long associated with depression; they are often used to identify newly presenting depressive patients, and may be part of a more general alteration of biological rhythms. Furthermore, persistent insomnia is a common residual symptom in incompletely remitted depression. As a rule, to avoid the recurrence of depressive symptomatology, treatment of associated insomnia should be pursued in patients taking antidepressants. Combining pharmacotherapy with nonpharmacological treatments that take into account the sleep-wake cycle (sleep deprivation, light therapy) could help in the resolution of both depressive symptoms and associated sleep disorders. A novel pharmaceutical agent, agomelatine, an agonist of melatonergic MT1 and MT2 receptors, as well as an antagonist of 5-HT2C receptors, shows a unique synchronizing effect on circadian rhythms and demonstrates robust antidepressant efficacy.

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Keywords: insomnia; sleep disorder; slow-wave sleep; rapid eye movement; incomplete remission; circadian rhythm; psychotherapy; pharmacotherapy

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Mechanisms for sleep changes in depression

Sleep mechanisms and the pathophysiology of depression are closely interrelated. Monoaminergic and cholinergic neurotransmission are heavily involved in both. Therefore, it is not surprising that depression is almost invariably associated with sleep abnormalities. Several hypotheses have been proposed to explain their occurrence. The first hypothesis suggests that an imbalance between the monoaminergic and cholinergic systems in the central nervous system could be responsible for both the pathophysiology of depression and the observed sleep aberrations. According to another hypothesis, increased pressure of REM sleep might be responsible; however, a number of medications (bupropion, nefazodone, and trazodone) with well-documented antidepressant efficacy do not suppress REM sleep, which suggests that REM sleep suppression might not be necessary for an antidepressant treatment response. The third hypothesis proposes an hypothalamic-pituitary-adrenal axis dysregulation.

The last hypothesis suggests that a deficiency in the mechanism responsible for non-REM sleep, as explained by the two-process model of sleep regulation, may be implicated. According to Borbély, the interaction of two processes is responsible for sleep regulation: a homeostatic process (process S), with an increase of EEG slow waves during waking and an exponential decline during sleep, interacts with a circadian process (process C)—an internal clock—so that the timing and architecture of sleep is determined. It was proposed that process S is deficient in patients with depression. In fact, the clinical sleep disturbance of early morning awakening could be attributed to an impaired functioning of process S during waking or an earlier timing of process C. The fast antidepressant effect gained from sleep deprivation might arise from an increase in process S to normal levels. By contrast, the slow antidepressant effect of a phase advance of the sleep-wake cycle might be related to gradual shifts of process S toward a correct phase relationship with regard to process C. However, it should be noted that the antidepressant effect of phase advance has not been confirmed in all studies. Moreover, decline of either process S during sleep or of the phase and amplitude of process C are other possible abnormalities that might be involved in sleep disturbances.

Circadian rhythms in depression

The biological clock in the suprachiasmatic nucleus (SCN), a master pacemaker driving circadian rhythms in the brain and body, is synchronized to the external light-dark cycle via retinal light input. Nocturnal synthesis of the pineal hormone melatonin is driven by the SCN. Yet, circadian oscillators are found in every organ, and each organ has its own appropriate synchronizer. Although light is the major synchronizer for the SCN, it does not affect clocks in the liver; the synchronizer for the latter is food, but food is not a synchronizer for the SCN. Individuals have different preferences for timing their sleep; some like to go to sleep early and wake up early in the morning, while others go to sleep late and wake up late. In addition, individual genetic characteristics of the molecular mechanisms of the biological clock might determine features of mood disorders, including age at onset, recurrence, symptoms of insomnia and response to its treatment, and response to sleep deprivation. Furthermore, it has been proposed that there is an intimate relationship between the neurotransmitter systems targeted by drugs and the circadian rhythms targeted by chronotherapeutics. These genetic factors may actually provide a chronobiological vulnerability for depression; in this case, a “double desynchronisation” may occur—“internal desynchronisation” between different clocks in the body and brain, and “external desynchronisation” between the timing of body rhythms with respect to the light-dark cycle.

Stable internal and external phase relationships appear to be crucial for a stable mood state (ie, the timing between cortisol and temperature body rhythms as well as the timing of sleep with respect to the day-night cycle). Any desynchronization might cause mood disturbances, particularly in vulnerable individuals. Certain synchronizers have been used to stabilize phase, with light and melatonin being the most important, but also sleep deprivation having been successfully applied in everyday practice.

Treatment considerations

- Nonpharmacological interventions on circadian rhythms
  Manipulations of the sleep-wake cycle, whether its duration (total or partial sleep deprivation) or its timing (partial sleep deprivation, phase advance), have profound and rapid effects on depressed mood in 60% of all diagnostic subgroups of affective disorders. The therapeutic effect of sleep deprivation is postulated to be linked to an increase in homeostatic sleep pressure; additionally, sleep deprivation-induced sleepiness may counteract the hyperarousal state that is often present in depression.

  Though sleep deprivation may have a transient effect on mood, it should always be considered as an option, since it might be the most rapid antidepressant therapeutic solution; however, most patients tend to relapse soon after recovery of sleep. The combination of sleep deprivation with lithium (with or without light therapy) or pindolol may prevent relapse.

  Light therapy was specifically developed as a synchronizer in the treatment of patients with seasonal affective disorders; however, it has also shown efficacy in nonseasonal depression, and it can prevent relapse after sleep deprivation. Bright light has three major effects on the circadian system: it increases circadian amplitude, shifts circadian phase (depending on the time of its application), and thereby modifies the phase relationships between the internal clock and sleep, and the external light-dark cycle. As mentioned, it has been reported that bright light can prevent relapse after sleep depriva-
Improvement of the sleep-wake cycle as a target for remission in depression – True Remission in Depression: The Ultimate Goal

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There is evidence from studies of primary insomnia that cognitive behavioral therapy (CBT) results in improvements that are as substantial as those of pharmacotherapy with sedative-hypnotics.47 The greatest advantage of CBT is that its effectiveness is more durable than that of pharmacotherapy and the benefits persist after therapy is terminated.48 CBT has also been reported to be efficient in the management of depression.49 Further research, however, is needed regarding the efficacy of CBT—in combination with antidepressant therapy—for insomniac patients with major depressive disorder.50

Behavioral modification of social rhythms may help in the treatment of depression. Frank and colleagues developed the Interpersonal and Social Rhythm Therapy (IPSRT) Intervention Program in order to establish regular social rhythm regularity (having regular bed, wake, and meal times, switching to a more regular work schedule, and incorporate a regular daily exercise session). IPSRT reduces the risk of recurrence in bipolar patients, regularizes social rhythms, accelerates remission in depressed patients, and lowers relapse rates; these effects are comparable with those of intensive pharmacotherapy.51 Further studies should determine whether IPSRT should be used alone or as an adjunctive treatment in major depression.52

Psychopharmacological treatment approaches

Melatonin, exogenously administered, acts as a synchronizer of circadian rhythms and sleep (eg, in blind persons) but does not appear to have any major effects on mood.53 Antidepressants alleviate symptoms of depression by altering the levels of various central nervous system neurotransmitters that are also involved in sleep regulation, and may have a considerable impact on sleep patterns. In general, the majority of antidepressant drugs suppress REM sleep and increase REM latency, although this is not always the case. As far as sleep efficiency and total sleep time are concerned, antidepressants can be distinguished as being either sedative or energizing.54 Currently-available antidepressants have notable limitations in terms of their only moderate efficacy compared with placebo, relatively slow onset of action, possible withdrawal symptoms, and problems of compliance. Sleep disturbances are often used to identify newly presenting depressive patients, and may be part of a more general alteration of bodily rhythms.55 Persistent insomnia is one of the most common residual symptoms in incompletely remitted depression.56

Residual depressive symptoms are one of the predictors of subsequent relapse risk,57,58 and of persistent functional disability. Complete relief of associated insomnia should be pursued in patients under treatment with antidepressants to avoid the recurrence of depressive symptomatology.59 In general, the sleep disturbances associated with depression improve as depressive symptom severity lessens with treatment, but different antidepressants have characteristic effects on sleep, particularly in the early stages of treatment.

On short-term administration, most tricyclic antidepressants (TCAs) promote sleep by increasing total sleep time and SWS. Furthermore, REM sleep suppression is reported with all TCAs except trimipramine.60,61 More specifically, amitriptyline, trimipramine, nortriptyline, dothiepin, and doxepin have all been associated with sedation (although imipramine62 and desipramine63 are less likely to be linked with sedation and have been associated with insomnia instead). Because of their sedative properties, these agents are often used as hypnotics in depressed patients suffering from insomnia.54-58 However, daytime drowsiness and poor functioning during the next day may be an untoward side effect of sedative TCAs, in particular amitriptyline and doxepin. It should also be noted that TCAs may cause insomnia by inducing or worsening periodic limb movement disorder, and that their use is often associated with nightmares.54

The reversible monoamine oxidase inhibitor moclobemide is associated with less REM sleep suppression and appears not to affect sleep notably.20 SSRIs are considered to be more energizing agents than other antidepressants. Although SSRIs are commonly associated with insomnia, sedation and daytime sleepiness have been occasionally reported with high doses of these drugs. Fluvoxamine and paroxetine have been reported as being more sedating than other SSRIs.22,26,67,68 Objective polysomnographic findings on the effects of SSRIs on sleep show prolongation of sleep onset latency, increased wakefulness, decreased sleep efficiency, increased number of arousals during the night, increased REM latency, and decreased total REM sleep, when compared with placebo and sedative TCAs.64-67,68 Furthermore, SSRIs can exacerbate periodic limb movement disorder and can cause nightmares. However, patients’ subjective sleep ratings whilst taking SSRIs are frequently positive. The same is also true in terms of clinicians’ ratings of sleep items on the Hamilton Rating Scale for Depression in clinical trials that investigated citalopram, sertraline, fluoxetine, fluvoxamine, and paroxetine. However, it is unlikely that a depressed patient with a history of severe sleep disturbance will benefit more from SSR1I treatment than from the administration of more sedative antidepressants.

Venlafaxine,69-71, a serotonin and norepinephrine reuptake inhibitor (SNRI), decreases total sleep time and may cause insomnia in 4% to 18% of depressed patients. Also, its administration has been associated with REM sleep behavior disorder. Venlafaxine and duloxetine72 (another SNRI), as well as reboxetine, a noradrenaline and serotonin reuptake inhibitor, appear to have a similar profile to SSRIs regarding their influence on REM sleep and overall sleep architecture. Another antidepressant that may cause insomnia is bupropion, a dopamine and norepinephrine reuptake inhibitor.54,55,59,60 However, patients’ subjective sleep ratings whilst taking venlafaxine and duloxetine are frequently positive. The same is also true in terms of clinicians’ ratings of sleep items on the Hamilton Rating Scale for Depression in clinical trials that investigated citalopram, sertraline, fluoxetine, fluvoxamine, and paroxetine. However, it is unlikely that a depressed patient with a history of severe sleep disturbance will benefit more from SSR1I treatment than from the administration of more sedative antidepressants.
reuptake inhibitor, which also decreases REM sleep and lengthens REM latency.

Trazodone, a serotonin, α1-adrenergic, and histamine receptor blocker, increases total sleep time, enhances SWS, and may cause excessive daytime sleepiness. Trazodone does not suppress REM sleep. It is a very sedative antidepressant and has often been used for the management of severe insomnia in depression. A number of trials have shown that trazodone is more effective than the TCAs and equally as effective as a hypnotic agent, zolpidem, in improving sleep. Nefazodone, a compound closely related to trazodone, is a potent antagonist of postsynaptic 5-HT2 receptors, but with a less potent α1-adrenoreceptor-blocking activity and no affinity for histamine receptors. It promotes sleep without suppressing REM sleep. Its pharmacological profile makes it one of the best antidepressants to relieve insomnia in the context of depression, and it is widely used as an adjunct to SSRIs and SNRIs.

Also, maprotiline, which acts by inhibiting reuptake of norepinephrine and blocking the histamine receptor, causes sedation and suppresses REM sleep. Similarly, amoxapine, which blocks the serotonin and histamine receptors and inhibits the uptake of norepinephrine, is another antidepressant that causes sedation. Tianeptine, a glutamate modulator, enhances sleep continuity and ameliorates subjective sleep quality without significantly modifying REM sleep parameters.

Mirtazapine is a selective serotonin and α2-adrenergic receptor blocker, which also blocks histamine receptors (noradrenergic and specific serotonergic antidepressant). Potent antagonism of H1 receptors causes immediate, nonspecific sedative effects upon administration. Mirtazapine increases total sleep time and suppresses REM sleep. It is frequently used when sleep complaints are a major concern in depression and its efficacy is comparable to that of sedative TCAs.

Agomelatine, an agonist of melatonergic MT1 and MT2 receptors, as well as an antagonist of 5-HT2C receptors, uniquely combines circadian synchronizing effects with selective norepinephrine and dopamine augmentation properties in the prefrontal cortex, and demonstrates robust antidepressant efficacy. When administered in the evening, it advances circadian phase and directly increases sleepiness through thermoregulatory mechanisms. This promotes a rapid sleep onset, but is without any after-effects the following day. The drug does not raise extracellular serotonin levels, and that is why it does not produce any of the side effects (diarrhea, nausea, sexual dysfunction, insomnia) usually observed with SSRIs. Furthermore, agomelatine does not block histaminergic, α1-adrenergic, and muscarinic receptors, and as a result does not share the side effects of TCAs.

**Combination therapy**

There is evidence from everyday clinical experience, and a few controlled studies as well, that combining benzodiazepine hypnotics or nonbenzodiazepine selective gamma aminobutyric acid (GABA) type A receptor antagonists, such as zolpidem, zopiclone, eszopiclone, and zaleplon, with antidepressants from the beginning of therapy may result in a faster relief of the concomitant sleep disturbance, and thereafter bring about a faster improvement in depressive symptoms. Therefore, it is common practice to use such combinations for the initial management of insomnia in the context of depression. Benzodiazepines commonly used for the management of insomnia are lorazepam, temazepam, alprazolam, oxazepam, triazolam, diazepam, flurazepam, and midazolam. All benzodiazepines shorten sleep onset latency, increase total sleep time and stage 2 sleep, and suppress REM sleep and SWS. Excessive daytime sleepiness is a troublesome side effect, which is more pronounced with long-acting benzodiazepines. Development of tolerance and exacerbation of insomnia with rebound of REM sleep upon withdrawal is also a major concern. Nonbenzodiazepine hypnotics have a better pharmacological profile with fewer and milder side effects than the benzodiazepines, and are currently preferred for the treatment of sleep problems in affective disorders. Recently, ramelteon, a novel selective agonist of melatonin MT1 and MT2 receptors, was approved for the treatment of primary insomnia. In comparison with the other hypnotics, it is claimed that ramelteon has the advantage of no potential for abuse. However, experience with this novel hypnotic agent in the treatment of insomnia associated with depression is still limited.

In cases resistant to treatment, the combination of antidepressants and antipsychotics should be considered. Adding an antipsychotic to the patients’ daily regimen (ie, olanzapine) might alleviate sleep disturbances by increasing SWS.

**Conclusion**

Sleep disturbances often occur in depressed patients, and they may be used to identify newly presenting or recurrent episodes of depression. Moreover, persistent insomnia is one of the most common residual symptoms in incompletely remitted depression. Generally, complete relief of associated insomnia should be pursued in patients under treatment with antidepressants to avoid the recurrence of depressive symptomatology. Currently-available antidepressants have notable limitations, mainly relating to their only moderate efficacy relative to placebo. A combination of nonpharmacological interventions (sleep deprivation, light therapy, CBT, IPSRT) together with pharmacotherapy could be used to improve management of sleep disturbances associated with depression. A novel antidepressant compound, agomelatine, an agonist of melatonergic MT1 and MT2 receptors as well as an antagonist of 5-HT2C receptors, has been recently introduced; it shows a synchronizing effect on circadian rhythms and demonstrates robust antidepressant efficacy, while it produces a superior and earlier improvement in the sleep-wake cycle compared with other antidepressant agents. This sleep-restorative antidepressant offers the possibility of an improved quality of remission, while minimizing relapses or recurrences of depressive episodes.
REFERENCES
L’amélioration du cycle veille-sommeil comme cible de la rémission dans la dépression

Les troubles du sommeil sont associés depuis longtemps à la dépression ; souvent utilisés pour identifier les patients débutant une dépression, ils pourraient apparaître à une perturbation plus générale des rythmes biologiques. De plus, l’insomnie persistante est un symptôme résiduel fréquent d’une dépression incomplètement guérie. Afin d’éviter la récidive des symptômes dépressifs, il est de règle de poursuivre le traitement de l’insomnie chez les patients traités par antidépresseurs. L’association de traitements médicamenteux et non médicamenteux ciblant le cycle veille-sommeil (privation de sommeil, lumiorthérapie) peut contribuer à la disparition des symptômes dépressifs et des troubles du sommeil associés. L’agomélétine, une nouvelle molécule agoniste des récepteurs mélatoninergiques MT1 et MT2 et antagoniste des récepteurs 5-HT2C, possède un effet unique de synchronisation des rythmes circadiens et une bonne efficacité antidépressive.
Remission: concept and reality

Remission in major depressive disorder (MDD) typically refers to symptom remission; that is, the near absence of all pre-existing symptoms endorsed on an established rating scale for depressive symptoms.\(^1\) Virtually all studies on the treatment of a major depressive episode utilize either the 17-item Hamilton Rating Scale for Depression (HAM-D\(_{17}\))\(^2\) or the Montgomery–Åsberg Depression Rating Scale (MADRS)\(^3\) to assess remission. For the HAM-D\(_{17}\), a score of 7 or less to connote remission has achieved the greatest acceptance.\(^4\) On MADRS, scores of 10 or less, or in some instances 12 or less, have been advocated to reflect remission.\(^5,6\)

Evidence shows that there is variation among remission rates for different antidepressants and in different patient populations. Higher remission rates have been reported with venlafaxine (40%-45%) compared with selective serotonin reuptake inhibitors (SSRIs; 35%-40%) in some,\(^7,8\) but not all, meta-analyses of randomized controlled trials.\(^9,10\) Patients in effectiveness trials typically achieve even lower rates of remission. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,\(^11\) only 28% of patients who received citalopram (SSRI) for up to 14 weeks met remission criteria.

Failure to achieve remission is associated with many adverse consequences, including high rates of recurrence, decreased work productivity, greater medical comorbidity, and an overall decrease in quality of life.\(^4,12\) Even patients treated to remission report a substantial burden of subthreshold or threshold symptoms: insomnia (44%), fatigue (38%), and anhedonia (27%) were the most prevalent residual symptoms in fluoxetine-treated remitters,\(^13\) while anxiety and loss of libido were also prevalent in other patient populations following remission.\(^14,15\) Although clinically meaningful, a limitation in the concept of remission is that it may not fully reflect the patient’s perspective regarding the balance between symptom change, side effect burden, and functional outcome. Patients reported “presence of positive mental health,” “return to one’s usual normal self,” and “return to usual level of functioning” as the three most important items in determining remission.\(^16\)

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition Text Revision</td>
</tr>
<tr>
<td>HAM-D(_{17})</td>
<td>17-item Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases and Related Health Problems - 10th Edition</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery–Åsberg Depression Rating Scale</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>SSR1</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>STAR*D</td>
<td>Sequenced Treatment Alternatives to Relieve Depression (study)</td>
</tr>
</tbody>
</table>
Lack or loss of sexual desire
Failure of genital response
Premature ejaculation
Orgasmic dysfunction
Nonorganic dyspareunia
Nonorganic vaginismus
Sexual aversion and lack of sexual enjoyment
Unspecified sexual dysfunction, not caused by organic disorder or disease

Quality of life as an expanded concept

By assessing a patient’s overall sense of satisfaction and personal wellbeing, quality of life measures reflect outcomes beyond symptom improvement. Patients with MDD may experience limitations in the areas of physical health, work efficiency, and social interactions. Measures have been developed for use across a wide range of disorders and populations (e.g., Euro Quality of Life-5D, Short-Form 36-Item Questionnaire), across different psychiatric populations (e.g., Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction Questionnaire), or specifically, in depressed patients (Social Adaptation and Self-Evaluation Scale).17 These scales have been valuable in demonstrating that psychosocial impairment persists in MDD even beyond remission,18,19 indicating that symptom improvement and quality of life do not necessarily improve at the same rate. When MDD patients were evaluated periodically over 5 years of treatment, marital and sexual satisfaction ratings were persistently lower compared with controls.20 Achieving symptomatic remission has to be partnered with minimal side effects to attain the best treatment outcome. This was recognized as an important issue by psychiatrists, who ranked sexual dysfunction as the highest consideration in prescribing an antidepressant, followed by weight gain and fatigue (Table I).21

Sexual dysfunction as a component of remission and quality of life

In addition to sleep and alertness22 and neurocognitive symptoms,23 healthy sexual function is an important component of good quality of life, yet sexual dysfunction is a frequent consequence of antidepressant therapy,24,25 and is unacceptable to many patients. In a large study involving over 6000 patients who received antidepressant therapy, 85% rated sexual functioning as “extremely important,” “very important,” or “important,” while only 5% felt it was “not important.”26 Unfortunately, sexual dysfunction is a relatively neglected aspect of both remission and quality of life, despite its simple measurement, high prevalence, and negative impact on treatment adherence.

Classification and measurement

The International Classification of Diseases and Related Health Problems—10th Edition (ICD-10)27 lists 10 forms of sexual dysfunction (Table II), which can be associated with physical or psychiatric conditions, medication treatments, or psychosocial factors. Sexual dysfunction in MDD typically involves problems with desire, arousal or orgasmic/ejaculatory function, and may occur across several of these areas. While the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition Text Revision (DSM IV-TR) does not explicitly include loss of sexual interest or desire as a core item, clinicians consider libido as a component of “diminished interest or pleasure,” and a single item on HAM-D17 captures desire or interest in sex as a component of overall symptom severity. However, this scale does not assess the broader impact of sexual dysfunction on quality of life.

The issue of measurement across the spectrum of sexual dysfunction is of particular importance when considering the adverse impact that SSRIs and other antidepressants can have on diverse areas of sexual function.28,29 Several easy to use sexual function scales are available (Arizona Sexual Experience Scale, Changes in Sexual Functioning Questionnaire, Psychotropic-Related Sexual Dysfunction Questionnaire, and the Sex Effects Scale).25 The importance of administering direct assessment scales is underscored by the findings that symptom reports increase twofold (69%) with direct questioning compared with reliance on spontaneous self-report (35%).26

Prevalence and risk factors

The prevalence of sexual dysfunction in the community is estimated to be approximately 20%-30%31,32; a considerably higher prevalence rate of 50% or more has been reported in untreated depressed patients, and even higher rates are reported during antidepressant treatment.33 Risk factors for sexual dysfunction among psychiatric inpatients include: (i) history of physical, emotional, and sexual abuse; (ii) self-harm and depression; (iii) poor self-rated health and cardiopulmonary conditions; and (iv) use of antidepressants.33

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**Table I. Symptoms influencing psychiatrists’ antidepressant choice for outpatients.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual dysfunction</td>
<td>231</td>
<td>20</td>
</tr>
<tr>
<td>Weight gain</td>
<td>201</td>
<td>18</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107</td>
<td>9</td>
</tr>
<tr>
<td>Anticholinergic effects</td>
<td>82</td>
<td>7</td>
</tr>
<tr>
<td>Agitation</td>
<td>73</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>


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**Table II. Classification of sexual dysfunction according to the International Classification of Mental and Behavioural Disorders—10th edition.** Based on data from reference 27.

- Lack or loss of sexual desire
- Sexual aversion and lack of sexual enjoyment
- Failure of genital response
- Orgasmic dysfunction
- Premature ejaculation
- Nonorganic vaginismus
- Nonorganic dyspareunia
- Excessive sexual drive
- Other sexual dysfunction, not caused by organic disorder of disease
- Unspecified sexual dysfunction, not caused by organic disorder or disease
Adherence and discontinuation

Treatment-emergent sexual dysfunction can cause significant distress to depressed patients, which adversely affects quality of life and leads to antidepressant nonadherence. Sexual dysfunction was the most bothersome side effect in a survey of more than 400 patients treated with SSRIs for approximately 3 months. Beside being a troublesome adverse event, sexual dysfunction is also one of the most common side effects leading to treatment discontinuation during short-term and long-term care. Further supporting this finding, Rosenberg and colleagues reported that 42% of men and 15% of women discontinue antidepressant treatment over perceived beliefs about sexual side effects.

Managing drug-induced sexual dysfunction in remitted patients

In order to reduce treatment nonadherence, several strategies can be used to mitigate treatment-emergent sexual dysfunction, including augmentation with an antidote, switching medications, or preferably prescribing an antidepressant with fewer sexual side effects in the first instance. Although primary prevention is the optimal solution, this is not always possible in the treatment of MDD. Several antidepressants are associated with treatment-emergent sexual dysfunction in less than 10% of patients, while others result in significant impairment in 30% or more patients (Table III). These differences have been linked to putative neurotransmitter and neuropeptide abnormalities associated with sexual dysfunction, and the beneficial or adverse effects of various antidepressants on these targets. Four mechanisms associated with drug-induced sexual dysfunction involve: (i) decreased dopaminergic activity; (ii) agonism of 5HT2 and 5HT3 receptors; (iii) blockade of adrenergic and cholinergic receptors; and (iv) inhibition of nitric oxide synthase. Various antidotes targeting one or more of these mechanisms have been advocated to mitigate these adverse effects.

Antidotes to mitigate sexual dysfunction

Enhancement of dopaminergic activity

Bupropion, psychostimulants, and amantadine have all been evaluated as treatments to relieve sexual dysfunction. In two out of three bupropion add-on studies, a dose of 150 mg versus placebo failed to improve sexual dysfunction associated with SSRIs, although augmentation with bupropion SR 150 mg twice daily was significantly better than placebo in improving desire and frequency of sexual activity in remitted depressed patients on SSRI therapies. It was also observed in an open-label augmentation study that bupropion not only improved sexual dysfunction in venlafaxine-treated patients, but also increased blood levels of venlafaxine approximately threefold. Stimulants such as methylphenidate have also been advocated to treat sexual dysfunction on the basis of their prodopaminergic effects. Although augmentation of antidepressant monotherapy with sustained release methylphenidate did not significantly enhance depression outcomes, there was a significant improvement in sexual function, as well as apathy and fatigue, compared with placebo. In clinical practice, other stimulants are used to enhance sexual function (dextroamphetamine, modafinil), but there are no randomized-controlled trials to support these recommendations. On a cautionary note, various dopamine agonists used to treat Parkinson’s disease (pramipexole, ropinirole, and pergolide) have been associated with pathological hypersexuality.

Antagonism of 5HT2A and 5HT3 receptors or agonism of 5HT1A receptors

Several antidepressants are known to display antagonistic effects at 5HT2 or 5HT3 receptors. In the case of mirtazapine, there was found to be no advantage over placebo when the drug was added to fluoxetine in depressed women experiencing drug-induced sexual dysfunction. There is preliminary evidence that mirtazapine added to duloxetine improves duloxetine-induced sexual dysfunction, and anecdotal support for cyproheptadine, a 5HT2 antagonist, particularly for anorgasmia, although granisetron, a 5HT3 antagonist, did not offer any advantage over placebo.

The potentially beneficial antagonism of 5HT2A and 5HT3 receptors by atypical antipsychotics is countered by other mechanisms likely to increase serotonergic output and exacerbate sexual dysfunction. Despite the increasing use of “atypicals” such as risperidone, olanzapine, aripiprazole, quetiapine, and ziprasidone to treat patients with mood disorders, only minimal attention has been paid to sexual function. There was found to be no significant advantage of olanzapine versus placebo in reversing antidepressant-induced side effects, and contradictory findings were reported in two small open-label studies using risperidone: a reduction in sexual function in one study and potentially beneficial effects in the other. The only systematic comparison of sexual dysfunction across atypical antipsychotics was performed in a large cross-sectional study involving more than 600 schizophrenia patients. Sexual dysfunction was reported in 43% of patients receiving risperidone, 35% on olanzapine, and 18% on quetiapine. Differences in diagnosis, underlying neurotransmitter function, dosing of atypical antipsychotics, and baseline sexual function limit the generalizability of these findings to the MDD population. Several agents with 5HT1A agonist properties have been evaluated as antidotes.

Table III. Frequency of sexual dysfunction during antidepressant treatment with different antidepressant medications. Based on data from reference 41.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Citalopram</th>
<th>Fluoxetine</th>
<th>Duloxetine</th>
<th>Fluvoxamine</th>
<th>Paroxetine</th>
<th>Venlafaxine</th>
<th>Sertraline</th>
<th>Reboxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>&lt;10%</td>
<td>10%-30%</td>
<td>&gt;30%</td>
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<tr>
<td>Bupropion</td>
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<td>Milnacipran</td>
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<tr>
<td>Mirtazapine</td>
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<td></td>
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<tr>
<td>Moclobemide</td>
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<td></td>
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<tr>
<td>Reboxetine</td>
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</tbody>
</table>

Kennedy and Rizvi
for sexual dysfunction. The anxiolytic, buspirone, has shown to improve SSRI-induced sexual dysfunction, with more pronounced effects in women than men.60 Though thioridazine failed to demonstrate antidepressant efficacy, this 5HT1D agonist and 5HT2A antagonist with minimal DA4 agonist effects67 has been evaluated for the treatment of Hypoxic Sexual Desire Disorder in women, with positive results.56 VML-670 is a novel 5HT1D agonist with weak 5HT1D agonist properties. It was not superior to placebo in overall improvement of sexual dysfunction in previously depressed male and female patients.59

Blockade of adrenergic and cholinergic receptors

Yohimbine is an α-adrenergic agonist with favorable anecdotal evidence about its role in treating sexual dysfunction, but negative results under placebo-controlled conditions.68 Bethanecol has mixed central and peripheral cholinergic and adrenergic effects. It was effective in reversing clomipramine-induced ejaculatory delay under placebo-controlled conditions.69

Inhibition of nitric oxide synthase

The largest trials and most robust evidence for reversal of SSRI-induced sexual dysfunction involve treatment with sildenafil, the prototypic phosphodiesterase inhibitor. Sildenafil in doses of 25-100 mg has been shown to significantly enhance sexual function in both men61,62 and women63 treated to remission with SSRIs. Preliminary evidence also supports the role of tadalafl in reversing SSRI-induced sexual dysfunction in both men64 and women.65

Comparison of sexual dysfunction across antidepressant monotherapies

Sexual dysfunction is a significant problem with first generation monoamine oxidase inhibitors and tricyclic antidepressants, although other adverse effects have been of much greater clinical concern. The consensus from a series of well-designed comparative studies is that up to 60% of patients receiving SSRIs report some form of treatment-emergent sexual dysfunction.24,28,66-71 All of the SSRIs have been associated with delayed or absent orgasm/ejaculation, and in some instances, a reduction in libido and arousal.28,72,73

Similar rates of sexual dysfunction have been reported with serotonin norepinephrine reuptake inhibitors,23,24 although some evidence supports a lower rate with duloxetine, desvenlafaxine, and milnacipran, potentially related to greater noradrenergic blockade.74-77 Reboxetine is the only second generation norepinephrine receptor inhibitor, and is not widely available as an antidepressant. Nevertheless, it is associated with a relatively favorable sexual function profile compared with SSRIs.75

Among antidepressant monotherapies with the least likelihood of inducing sexual dysfunction, other variables beyond efficacy need to be considered. In the case of mirtazapine, switching to this from an SSRI resulted in lower rates of sexual dysfunction,78 but other adverse effects including weight gain and daytime sedation resulted in high rates of discontinuation.79 Nefazodone, a 5HT1 receptor antagonist and norepinephrine reuptake inhibitor, was relatively sparing of sexual function,80 but is now largely unavailable because of hepatotoxicity concerns.81 Bupropion, with its synergistic effects on dopamine and norepinephrine systems, results in less sexual dysfunction than SSRIs10 or venlafaxine.82 Similarly, moclobemide, a reversible inhibitor of monoamine oxidase A, has a favorable impact on sexual dysfunction, although it is not generally considered to be a first-line antidepressant.23,83,84

Agomelatine, a novel antidepressant with direct agonist effects on the melatonergic MT1 and MT2 receptors, as well as 5HT2C antagonist properties,25 has favorable effects on sexual function. Both mechanisms may synergistically account for its lack of sexual dysfunction, since agomelatine exerts putative antagonistic effects on 5HT2 receptors, which are in turn involved in sexual behaviour.85 In addition to antidepressant efficacy,24,84 agomelatine has been evaluated in depressed patients and healthy volunteers with sexual function as a primary outcome measure.86 Among sexually active remitted patients, there was significantly less treatment-emergent sexual dysfunction in patients receiving agomelatine compared with venlafaxine, specifically in the domains of sexual drive/desire in men and orgasm in women. This was illustrated by significantly greater deteriorations on the Sex Effects scale with venlafaxine for sexual drive/desire in men and orgasm in women (an approximately fivefold difference compared with agomelatine for both).1 In other agomelatine trials in which the Arizona Sexual Experience Scale was used, the rate of sexual dysfunction with agomelatine was comparable to or lower than that reported in the placebo group. These results are supported by a study carried out in healthy male volunteers who were randomized to receive agomelatine, paroxetine, or placebo for 8 weeks. The percentage of volunteers who experienced severe or moderate sexual dysfunction was under 5% for agomelatine, 62% for paroxetine, and 0% for placebo.86

Conclusion

The narrow clinical concept of remission, while valuable in a number of ways, fails to capture the broader domains associated with good quality of life. Healthy sexual function is an important outcome for patients with MDD, yet the majority of currently prescribed antidepressants induce or exacerbate sexual dysfunction. While there are various pharmacological approaches to mitigate drug-induced sexual dysfunction, prescribing a first-line antidepressant treatment that respects sexual function is a preferred approach.

REFERENCES

TRUE REMISSION IN DEPRESSION: THE ULTIMATE GOAL

Fonction sexuelle et qualité de vie des patients après rémission d’une dépression

L’adoption de la rémission comme critère clinique dans le traitement des troubles dépressifs majeurs (TDM) a permis de souligner l’importance des conséquences négatives des symptômes résiduels après un traitement antidépresseur, comme le montrent les différences de perception de la rémission entre les médecins et les patients. Il est donc nécessaire d’élargir les critères d’évaluation afin de mieux mesurer la qualité de vie des patients qui ont été traités pour des TDM. Les troubles sexuels sont souvent rapportés comme symptômes du TDM et sont plus souvent encore la conséquence de nombreux traitements antidépresseurs actuels. Pour beaucoup de patients dépressifs, la dysfonction sexuelle entraine une détérioration de la qualité de vie, une non observance du traitement puis son arrêt. De nombreux antidotes ont été proposés pour soulager les troubles sexuels dus aux antidépresseurs, mais très peu peuvent être recommandés sur la base d’études contrôlées randomisées fiables. La meilleure stratégie consiste donc dans la prescription d’une monothérapie (un seul antidépresseur) qui respecte la fonction sexuelle.
Emotional blunting or reduced reactivity following remission of major depression

by J. Price and G. M. Goodwin, United Kingdom

Antidepressants such as the selective serotonin reuptake inhibitors are used widely to treat major depression. While they have reasonable efficacy, they also produce adverse effects. The best known of these relate to physical effects like nausea and the impact on sexual function. However, anecdotally there appears to be a broader impact on emotional experience. This is usually described as a reduction in sensitivity or a sense of numbing or blunting, which may emerge as depression remits. While it may be confounded by the residual effects of depression, patients often attribute it to their medication. We propose that this phenomenon of emotional side effects of antidepressants requires further study. There is laboratory evidence to relate it under experimental conditions to the processing of emotion. Reduced detection of negative emotion in the faces of others can be demonstrated in healthy volunteers who have taken citalopram or reboxetine for just 1 week. This effect may predict the clinical problems that we see. We have now also developed an assessment scale expressly for use in clinical studies. The future will be to look at antidepressants whose profile appears to be less emotionally blunting—like agomelatine and other medications now in development with novel mechanisms of action—in well-designed clinical studies that can illustrate the absolute and relative frequency of what is an increasingly troublesome side effect of current treatments.

Keywords: depression; emotional processing; sexual function; clinical trial; outcome assessment; SSRI; side effect; pharmacotherapy; antidepressant

Selected abbreviations and acronyms

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<th>Acronym</th>
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<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition</td>
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<td>LEIS</td>
<td>Laukes Emotional Intensity Scale</td>
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<td>OQESA</td>
<td>Oxford Questionnaire of Emotional Side effects of Antidepressants</td>
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<td>SNRI</td>
<td>serotonin and norepinephrine reuptake inhibitor</td>
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veals that little formal research has been done on antidepressant-associated emotional blunting. However, there has been a steady trickle of reports since 1990, when Hoehn-Saric and colleagues reported dose-dependent apathy, indifference, loss of initiative, and disinhibition in patients on fluvoxamine or fluoxetine.\(^1\) There have, for example, been further reports of SSRI-induced apathy, indifference, and reduced motivation in children, adolescents, adults, and older adults\(^5-8;\) of inability to cry\(^5;\) of reduction in irritability, aggression, and negative affect\(^6;\) and of reduced emotional lability resulting from cerebrovascular accident\(^12-14\) or other brain injury.\(^15,16\)

Opbroek and colleagues\(^7\) moved the field conceptually by linking the rating of a wider impact of SSRI\(s\) on emotion to effects specifically on sexual function. The Lauxes Emotional Intensity Scale (LEIS) was used in 15 participants meeting criteria for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition) major depression who reported SSRI-induced sexual dysfunction, and in a control group of 16 hospital employees. Compared with controls, the SSRI group reported significant reductions in 12 of the 18 LEIS items, including ability to cry, irritation, care about others’ feelings, sadness, erotic dreaming, creativity, surprise, anger, expression of their feelings, worry, sexual pleasure, and interest in sex.

However, the way in which emotional side effects should be understood, measured, and so definitively investigated has remained uncertain. We have recently investigated the nature of this phenomenon by conducting interviews with people who attribute emotional symptoms to their SSRI.\(^8\) This study provided evidence that some patients taking SSRIs experienced significant emotional symptoms that they strongly attributed to their antidepressant, and that had a demonstrable impact on their functioning and played a role in their decision making about ongoing antidepressant adherence. These emotional symptoms could be described within six key themes—general effects on all emotions, reduction in positive emotions, reduction in negative emotions, emotional detachment, just not caring, and a changed personality. These themes are expanded, and examples given, in Box 2.

**Epidemiology**

There are no good data to indicate the frequency of emotional side effects, when they are most frequent and most problematic, and whether they are more common with some currently available antidepressants than others. However, it is clear from Internet reports, our clinical experience, and our experience of recruiting patients to research studies, that emotional side effects are not uncommon, and that there is a spectrum of experience from mild side effects through to severe side effects that is the source of bitter complaint. Some patients report that they suffered emotional side effects only as they experienced remission, while others report that they experienced them throughout the period of antidepressant administration. While SSRIs appear to be most closely associated with emotional side effects,

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**Box 1. Patient descriptions of emotional blunting taken from the Internet. All rights reserved.**

**General effects on all emotions**
- Reduced intensity, or even absence of emotions, which are flattened, numbed, dulled or blanked; thoughts rather than feelings; difficulty understanding emotions; emotions feel fake or artificial; improved emotional control.

  “I think that’s because my brain isn’t in a place where it can feel stuff. I’m on this constant emotional plain of blank-blank—not happiness but OK-ness.”

**Reduction in positive emotions**
- Reduced intensity and frequency of, eg, excitement, enjoyment happiness, love, affection, passion, enthusiasm.

  “I’d be… aware that I was in a situation or doing something that… should make me happy but it would just have no real effect.”

**Reduction in negative emotions**
- Reduced intensity and frequency of, eg, sadness, anger, aggression, anxiety and worry. Reduced ability to cry.

  “A feeling of being depressed was like cycling over cobble stones and you’re feeling things a bit too intensely and too sharply … and the sort of flattening out effect of antidepressants is something which is cushioning that…”

**Emotional detachment**
- Detachment or disconnection from the environment; from the self; and from other people, including children, partner and friends.

  “I am able to comfort and cuddle [my children] but I feel that like there is no emotion behind it.”

**Just not caring**
- Not caring about self, about others, about responsibilities; apathy; reduced interest and motivation; disinhibition; thoughts of self-harm.

  “I… felt slightly removed from everything… I just left things; you know… things didn’t really matter somehow. And it was only really when I came off them I realised I’d sort of skated over so much in life… important issues weren’t so important.”

**Changed personality**
- Aspects of personality are altered or removed; behavior is out of character.

  “It does dull the edge of your responsiveness. So you end up wondering whether, and since your personality is made up of emotions, you feel that your personality has been shifted sideways or been unbalanced somehow.”

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**Box 2. Emotional side effects of selective serotonin reuptake inhibitors: key themes. Based on data from reference 18.**
other classes of antidepressant such as SNRIs and mood stabilizers such as lithium salts have also been described as doing the same thing.

**Impact on quality of life**

Little is known about the impact of emotional side effects on quality of life in remission. However, our recent qualitative study investigated this in a sample of patients with chronic antidepressant use (median duration 23 months) and modest levels of depression (median Beck Depression Inventory–II score 12.5). The impact of emotional side effects on participants’ daily lives varied widely, both in extent and in perceived helpfulness. Some participants described emotional side effects as being helpful. For example, the reduction of certain emotional responses, such as anger, aggression, or worry might benefit personal relationships. Furthermore, emotional detachment and reduced anxiety might enable a person to think more clearly and objectively about their life situation.

However, some participants were concerned that blunting of their emotions and, thereby, of their day to day concerns, might mask or hide problems. This might prevent them resolving their own emotional issues, prevent them engaging with other problems or issues requiring their attention, and “cover up” who they really were. “Just not caring” had an unhelpful effect on everyday responsibilities, resulting in financial problems and problems at work or college. Emotional detachment from family and reduced emotional responsiveness had an unhelpful impact on family life, and on perceived quality of parenting. Reduced inspiration, reduced imagination, reduced motivation, and reduced passion for and enjoyment of creative activities, had adversely affected some participants’ creativity. In some participants, emotional side effects had led to reduced sociability. Finally, emotional flattening, emotional detachment from other people, and reduced concern for other people’s needs and feelings had unhelpful effects on relationships within families, with a significant other, and at work.

**Assessment**

**Clinical assessment**

It is likely that emotional side effects are under-reported in clinical populations due to the lack of systematic enquiry by health care professionals. We recommend that clinicians ask routinely about emotional side effects when they are assessing progress with antidepressants. This might comprise asking a broad screening question, and then, if necessary, following up with more specific questions to characterize the nature and extent of the problem, the extent to which the patient attributes the problems to their antidepressant, and its contribution to their decision-making regarding ongoing adherence. An effective screening question might be: “Have you experienced any emotional side effects from your antidepressant? (prompt if required...)” Emotional side effects are varied, but might include, for example, feeling emotionally ‘numbed’ or ‘blunted’ in some way, lacking some positive emotions or negative emotions, feeling detached from the world around you, or ‘just not caring’ about things that you used to care about.”

**Scientific assessment: in the laboratory**

Changes in emotional processing can also be shown to accompany the administration of SSRI and SNRI drugs to healthy volunteers. By emotional processing, one means the capacity of subjects to identify either the emotional expression in the faces of others (a perceptual expression of emotional sensitivity) or to remember emotionally charged self-referent words. The SSRI citalopram given to healthy volunteers for 7 days and the selective noradrenergic drug reboxetine given for the same period of time both reduced the capacity of volunteers to accurately detect negative emotion in faces presented to them in an experimental paradigm. There was even a reduced signal in the amygdala in response to the same faces presented subliminally. This could imply that these individuals might be less sensitive socially to the expression of negative emotions by others. While this could be a helpful change in emotional processing with regard to both anxiety and depression, it could also, when patients have recovered, lead to a changed sense of the immediacy of experience.

Changes could also be demonstrated in the domain of emotional memory following the administration of antidepressants to healthy volunteers. In this case, subjects were more able to recall positive than negative adjectives that could refer to them. This effect may be interpreted as reflecting a potentially therapeutic change in how emotion is processed. However, in potential contrast with the perception of emotion in faces, it would not itself lead to a predictable change in emotional experience that would be likely to be negative. Therefore it is possible that one way to screen for the presence or absence of emotional blunting from any medication would be to compare the impact on a patient’s immediate judgment of emotional valence with the impact on how emotionally charged adjectives are recalled from memory. It is a strong hypothesis of the Oxford group that emotional blunting may be associated with the former, while antidepressant efficacy per se will be associated with the latter. Findings with the new antidepressant agomelatine, whose novel mechanism of action comprises melatonergic agonist activity at MT1 and MT2 receptors and antagonist activity at serotonergic 5-HT2C receptors, when given for 1 week to healthy volunteers, will be an important test: the further question will be whether these properties of agomelatine translate as we would predict into antidepressant efficacy without emotional blunting. However, to know if this occurs we will require a better measure of the clinical as opposed to the laboratory experience.

**Scientific assessment: in the clinic**

A sensitive and valid questionnaire measure of this phenomenon is needed. This would enable research into the prevalence of the emotional side effects of
antidepressants, and comparison of the extent to which individual antidepressants are associated with them. It could be an important outcome measure in clinical trials designed to compare different products. Such a measure needs to be carefully designed and validated. Unfortunately, the two existing measures that attempt to address this issue appear to lack either careful design or validation.

The first is LEIS, a self-report instrument comprising 18 questions asking patients to rate an aspect of their emotional life compared with their “usual” state according to a 5-point scale (a lot less/somewhat less/same as usual/somewhat more/a lot more). This scale is unvalidated, and the single published report of its use in an observational study gives few details about its development, stating only that “we systematically questioned patients treated with SSRIs about their subjective emotional experience before and after treatment,” and that “these unstructured interviews led to the development of a rating scale for SSRI-induced emotional blunting.”

The second is the Bell-Shipman Apathy/Emotional Blunting Questionnaire, which is described in the study report as “under development.” This self-completion questionnaire comprises five questions, each rated on a six-point scale from “strongly disagree” to “strongly agree,” which relate to aspects of four of the themes we identified—reduction in positive emotions, reduction in negative emotions, emotional detachment, and not caring. However, there are no published details of the development and selection of these questions, and no validation work appears to have been carried out. We have used the results of the careful observational work in our recent study to develop the Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQESA), which we have now piloted, refined, and validated in a sample of over 200 people taking antidepressants. The OQESA comprises 26 questions/statements in three sections. The respondent rates the extent of their agreement with each statement along a 5-point scale ranging from disagree to agree, according to their experience during the past week. Section 1 includes 12 statements relating to the respondent’s experience of emotional side effects during the past week (eg, “All my emotions, both ‘pleasant’ and ‘unpleasant,’ are ‘toned down’”). Section 2 includes 8 statements relating to experience of emotional side effects during the past week compared with the respondent’s experiences before they developed their illness/problem (eg, “Day to day life just doesn’t have the same emotional impact on me that it did before my illness/problem”). Within the 20 statements in Sections 1 and 2, the 4 dimensions, general reduction in emotions (GR), reduction in positive emotions (RP), emotional detachment from others (ED), and not caring (NC) are each represented by 5 statements. Finally, Section 3 comprises 5 statements regarding the extent to which respondents believe their antidepressant is responsible for their emotional symptoms (eg, “The antidepressant is preventing me from feeling my emotions in some way”), and a final statement regarding actual or contemplated non-adherence due to emotional side effects. A total score can be calculated, being the sum of the scores of the four dimensions, and represents the extent to which the respondent is affected by emotional side effects. If required, the further attributional dimension can be scored.

An important and, as yet, unanswered question is the extent to which emotional symptoms attributed to antidepressants are actually manifestations of residual depression, rather than being emotional side effects. Our validation data suggest that two of the four dimensions of the OQESA (RP and NC) may be closely related to depression as well as antidepressant-associated emotional blunting, whereas the other two dimensions (GR and ED) are less closely related to depression. We therefore recommend that, in high quality experimental work investigating emotional side effects of antidepressants, two subtotals are calculated—RP plus NC, and GR plus ED.

Conclusion

In summary, there is emerging evidence that one important adverse effect of SSRIs and related medicines is a negative impact on the processing of emotional experience. This was first described by patients themselves, and investigators are now catching up with the complaint by devising improved ways of measuring it, both experimentally and, perhaps most critically, clinically, by the use of an innovative scale. There is an appropriate and increasing emphasis upon the patient experience in judging the outcome of treatment with any intervention for mood disorder. In the case of antidepressants, the potentially negative effect on emotional experience is easily confounded with the symptoms of depression itself, but is a cause for concern and further research. It remains to be seen as to whether it proves to be an easy task to first devise the means to better measure the experience and second to develop treatments that will be effective in treating depression without producing the problem. The test of this will come from antidepressants with novel mechanisms of action, one of the first examples of which will be agomelatine.  

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T RUE R EMISSION IN D EPRESSION : T HE U LTIMATE G OAL


The term \textit{remission} has usually been applied to short-term achievement of low or absent symptom levels, representing an end to the immediate episode. The term \textit{recovery} has been used to reflect remis-
sion beyond this state, persisting for a longer time period, and being more complete. A further term, \textit{response}, has sometimes been used, implying consider-
able improvement, variously defined, but not necessarily to remission.

Even before recovery is fully achieved, relapse may occur. The term \textit{relapse} has been used in affective disorders particularly to describe an early return of the depressive episode after remission, up to approximately 9 months to a year following the acute episode. This has been assumed to be a return of the original illness. This assumption reflects views that were common in the early days of antidepres-
sants, ie, that the disorder is merely suppressed and that the underlying disturbance continues until spontaneous remission occurs. It is difficult to prove this theoretical distinction, other than by inferring it from the length of the symptom-free period. The term \textit{recurrence} has been reserved for development of a subsequent episode, assumed to represent a new episode.

Residual symptoms and relapse in depression

\textit{Residual symptoms indicating incomplete remission from depression present an important clinical problem. They occur in up to a third of depressed patients after acute treatment, and they span the typical symptoms of depression, except those of severe depressive disorder. Their most important consequence is a much increased risk of relapse, particularly in the first year. Residual symptoms point to the need for further acute treatment to produce greater improvement, if possible. They are a strong indication for longer than usual continuation treatment at an adequate dose, to prevent relapse. There is now also good evidence for cognitive therapy as an adjunct. Other persistent abnormalities after depression include social dysfunction, dysfunctional attitudes, hypothalamic-pituitary-adrenal (HPA) axis overactivity, shortened latency of rapid eye movement (REM) sleep, and mood lowering after trypto-
phan depletion. It is not clear how much some of these are associated with resid-
ual symptoms or occur independently, although continuing HPA axis overac-
tivity and shortened REM latency are also associated with increased risk of relapse. In addition, there is growing evidence for residual symptoms in bipolar disorder, particularly after bipolar depression, and for increased risk of relapse when they are present.}

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\textit{Partial remission and residual symptoms}

Missing from the original schema was consideration of an intermediate state, in which remission might be partial in degree, with residual symptoms, rather than complete. This has since emerged as being very important, as it has become clear that it is a key pointer to relapse and recurrence.
Residual symptoms received relatively little attention before the mid 1990s, but they are evident in some studies if the detail is examined, and some aspects were briefly reviewed. Indeed, clinical experience had long suggested that many patients improved only partially after initial treatment, leaving residual symptoms that persisted and fluctuated in the community, causing much disability. Because most studies grouped these patients either with those who had not remitted or with those who had relapsed, their proportion had not been very well documented.

A few studies described them separately. Among inpatients treated with amitriptyline, approximately one third were found to be complete responders, partial responders, and nonresponders, respectively. In a follow-up study to 4 years of a sample of female depressives who had responded to initial treatment with amitriptyline and had been included in a controlled trial of continuation antidepressant therapy and psychotherapy, many were still found to show moderate or fluctuating symptoms, corresponding approximately to residual chronicity, although these included some subjects who had relapsed and then remitted. Occurrence of residual symptoms was noted in general practice patients with depression and anxiety, and in 38% of elderly depressives at 1 year, and 20% at 2-4 years. We explored further the nature of these residual symptoms by examining individual symptom ratings. The residual symptoms were those typical of depression, with ratings at the level of moderate or greater on the Hamilton scale items of depressed mood, impairment of work and activities, psychic anxiety, and genial symptoms. The remaining depressive symptoms were present to at least a mild degree in most subjects, the exceptions being a group of symptoms typical of severe depression: late insomnia, retardation, agitation, hypochondriasis, weight loss, and loss of insight. A parallel set of ratings made at the initial assessment, we followed to remission or 15 months. Only 6% of the sample failed to remit to the criterion of 2 months below definite major depression by this point. However, on examining the findings in more detail, although the majority of remitters scored in the lower ranges of the 17-item Hamilton Rating Scale for Depression, an important proportion of 32% scored 8 or more on the Hamilton scale, 8 or less being the criterion proposed by Frank et al as indicating full remission or recovery. They spanned a range from 8 to 18, although they did not satisfy the criteria for major depression.

We also looked for initial predictors of later residual symptoms upon remission. Using an extensive set of ratings made at the initial assessment, we found very few significant predictors, and those that were found reflected higher initial severity. Patients with residual symptoms had higher initial scores on the Clinical Interview for Depression anxiety total score and on the Hamilton scale 17-item total score. Life events, social support, and expressed emotion did not predict residual symptoms. We also examined diagnoses made at the initial interview, using the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders–Third Edition Revised) criteria for dysthymia. Those patients with residual symptoms were not predominantly previous dysthymics. Only 11% of those with residual symptoms satisfied the DSM-III-R criteria for dysthymia, as opposed to 17% of those without residual symptoms. Residual major depression did not represent a return to dysthymia, but indicated a different phenomenon: persistence of the episode in spite of treatment.

We also examined treatment data, to explore whether deficient drug treatment might have been responsible for residual symptoms. This was not the case. In fact there was a general trend for patients with residual symptoms to be receiving higher rather than lower levels of treatment. This would be expected in a naturalistic follow-up, with good treatment assignment in practice based on the presence of more symptoms. It does not mean that higher treatment levels would not be beneficial, but does indicate that the symptoms were not a consequence of failure to give standard treatment.

More recent studies of residual symptoms have been reviewed by Fava et al. They have been reported both after drug treatment and psychotherapy. Fava et al, in a study of their own, reported a strong relationship between prodromal and residual symptoms. The most common symptoms were irritability and anxiety. The large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which reported higher non-remission rates for depression than were hitherto thought to occur, did not use a criterion for partial remission. Residual symptoms also comprise one aspect of the subthreshold depressive symptoms described in a number of long-term longitudinal studies. There is also another meaning of the term, to refer to minor symptoms occurring below the level of partial remission. For example, one or more residual symptoms were found to be present in 82% of elderly depression remitters who achieved a score of below 8 on the Hamilton depression scale. Among responders to fluoxetine scoring 7 or less on the Hamilton scale in another study, residual symptoms were frequent, particularly sleep disturbance, fatigue, loss of interest, and guilt. At these severity levels, the subjects would be below the usual threshold for partial remission. Possibly the majority of recovered depressives have these symptoms, but they overlap, probably to a considerable but so far...
ill-explored extent, with what is experienced in normality. These minor symptoms are not the subject of this paper, which concerns more definite incomplete remission.

Residual symptoms and relapse

Following remission, the patients in our original study were followed for another 15 months. As in other follow-up studies, there was a high rate of subsequent relapse, with 40% of subjects relapsing over the next 15 months. All the relapses occurred in the first 10 months, giving some support to the concept of relapse as an early phenomenon that is distinguished from recurrence later in time.

An important finding emerged when we separated out the subjects with residual symptoms at remission. Among these, 76% relapsed in the next 10 months compared with 25% of subjects without residual symptoms (Figure 1). Residual symptoms were a key predictor of subsequent relapse.

Other studies have found high relapse rates in residual depressives. One study found that patients with residual symptoms of depression obtained greater benefit from maintenance antidepressant therapy than those who had completely recovered. Prien and Kupfer found that relapse was less common after full remission of at least 16 weeks, a finding on which they based a recommendation that continuation treatment should comprise at least 4 months of complete remission. In another study, after 9 months, 49% of a Dutch sample were found to be in full remission and 45% in partial remission. The patients with residual symptoms relapsed early, mainly in the 4 months after remission, while those without these symptoms had further episodes that occurred at later than 1 year. Another study reported that major depressives with residual symptoms relapsed three times faster than those without. Residual symptoms have been found to be a strong predictor of relapse in primary care depressives. In Spanish depressive outpatients, a relapse rate of 67% was found in the 2 years following partial remission, as opposed to 14% after full remission. One study looked for the best definition of rating scale scores at 3 or 6 months that could predict later relapse. No precise cut-off score with good sensitivity and specificity was found, but the higher the score, the more likely was subsequent relapse.

There have been fewer studies of whether residual symptoms at remission predict longer-term recurrence, although some of the above studies fused earlier relapse and later recurrence in their reports. We later extended our original follow-up study to 10 years. The subjects with previous residual symptoms spent more time with depressive symptoms over the follow-up, but not more time at the full criteria for major depression, and they showed greater impairment in social adjustment. No significant differences were found between the two groups in the percentage having a recurrence in the long term, the mean number of recurrences, re-admissions, or chronic episodes, or clinical global outcome criteria, although there were small differences toward a worse outcome on these criteria. The effects of previous residual symptoms tended to decay over time, and more of the subjects achieved full remission in due course.

In a trial of maintenance imipramine and interpersonal therapy in patients who had achieved stable remission, the level of residual symptoms did not predict long-term outcome, but subjects with greater variability of residual symptoms had a higher risk of recurrence. In a similar trial in elderly patients, residual anxiety and residual sleep disturbance independently predicted early recurrence.

The treatment of residual symptoms and prevention of relapse

The most important implications of residual symptoms are the impaired future prognosis and the need for treatment. There are two aspects to the latter: treatment of the residual symptoms themselves and prophylactic treatment to prevent relapse.

Figure 1. Proportion of patients with (a) and without (b) residual symptoms relapsing after remission from depression.


The association with relapse argues strongly that residual symptoms should be treated vigorously in order to abolish them, although there is not conclusive proof from controlled trials that abolishing or diminishing them in vulnerable subjects will lower the risk of relapse. In any case, these are distressing symptoms, associated with poor role function and impact on families, and they need treatment in their own right. However, converting partial remission in these subjects into complete remission may not be easy. There is often a history of treatment with a variety of antidepressants in succession in the current and previous episodes, with only partial improvement, and with side effects limiting the doses that can be achieved.

There is little randomized controlled trial evidence regarding the efficacy of different antidepressants and other treatments for residual symptoms, and tentative recommendations therefore depend on general principles. As always, when response is limited, there should be a process of reassessment.
A careful history will often reveal the antidepressant that helped most in this episode or previous episodes, and that might be used in an increased dose. Care should be taken before concluding that a dependent personality is preventing full remission; chronic illness can create a misleading impression about a personality, which once full remission is achieved, is revealed to be robust. Assessment of the current situation may reveal perpetuating factors, such as family that has adjusted to the chronic illness by substituting for the patient’s roles, so that these are not available for the patient to return to without therapeutic work to change family expectations; or a spouse who needs the patient to be ill; or elements of secondary gain in the patient, such as compensation or insurance payments.

The second treatment aspect is the prevention of relapse and recurrence in these patients, whose risk is substantial. Here the evidence base is strong. A key aspect is continuation and maintenance medication, the general value of which is supported by many controlled trials. Earlier, a recommendation was made that continuation treatment should not be withdrawn until the patient had experienced 4 months free of all symptoms. This recommendation for routine circumstances may in fact be too short in the light of later evidence that the risk of relapse extends longer than previously thought. Nine to 12 months now seems a better length for routine continuation. However, the presence of residual symptoms sufficient to indicate incomplete remission indicates a need for longer continuation. Treatment should be continued if possible until they have become of minor degree or completely subsided, probably for at least 18 months. This may entail quite long-term continuation or maintenance. When treatment is withdrawn, withdrawal should be slow. If symptoms return or worsen as doses are reduced, the full dose should be resumed for a longer period. If breakthrough symptoms recur as the dose is reduced, this may argue for indefinite maintenance.

There is also good evidence for the efficacy of cognitive therapy in reducing relapse rates, particularly in the situation of residual symptoms. Seven controlled trials have shown reduced relapse rates, including two studies in residual depression. Our own study specifically targeted subjects with residual symptoms in spite of antidepressant treatment as being a relapse-prone group that needed treatment additional to antidepressants. We found that adding cognitive therapy to full doses of antidepressant continuation and maintenance lowered relapse rates (Figure 2), and the effect lasted for 3 and a half years after the end of the cognitive therapy. This appeared to be a specific effect on relapse: residual symptom levels themselves were not lowered. The evidence is now sufficiently strong that cognitive therapy should routinely be used as adjunctive treatment to medication when partial remission persists without conversion to full remission.

Other residual phenomena

Israel suggested that recovery from depression should be determined in three domains: symptoms, psychosocial function, and pathophysiological changes. Social dysfunction and disability are additional important consequences of a depressive episode. Social adjustment was evaluated longitudinally in the late 1960s in a sample of depressed women in New Haven, Connecticut, USA, comparing them with a matched group of normal subjects in the general population. Widespread impairment was found in the depressed group compared with normal subjects, extending across all the domains studied, including work, social and leisure activities, relationships with extended family, marital relationships, and parental function. These deficits remitted more slowly than did depressive symptoms, and in the 2-month time period that included
response and remission, these deficits were still severe. Improvement in some aspects was incomplete even at 8 months. Work impairment translates to decreased productivity and absence from employment, producing some indirect economic costs of depression. The problems associated with parental role are particularly important, since problems in parenting and parent-child relationships impact on development and later adaptation of the next generation.

Residual social dysfunction has since been reported by many other investigators and has been found to correlate with symptom outcome. Some of the many studies have been reviewed by Fava et al. Residual symptoms are associated with increased social dysfunction. In unpublished data derived from our controlled trial of cognitive therapy in patients with residual symptoms, we examined mean total scores on the Social Adjustment Scale at 20 weeks. Subjects with residual symptoms at 20 weeks and subjects who had relapsed by 20 weeks both showed worse social adjustment than those with neither adverse outcome at this point. Whether impaired social adjustment makes an independent contribution to prediction of subsequent relapse has not so far been reported.

A number of biological and neurocognitive measures, reviewed by Bhagwagar and Cowen, have been found to be abnormal in recovered depressives. Most prominent have been abnormalities of the hypothalamic-pituitary-adrenal axis, including waking salivary cortisol and dexamethasone non-suppression. The latter has been found to predict relapse. Several studies that followed up patients treated with tricyclic antidepressants found that dexamethasone non-suppression at the time of discharge predicted a greater risk of early relapse. One study of outpatients and two of patients treated with electroconvulsive therapy failed to find this. The enhanced dexamethasone–corticotropin-releasing-hormone test has also been found to predict relapse.

A second set of persistent biological abnormalities is related to serotonin. The most prominent of these is a return of depressive symptoms on depletion of tryptophan by a high amino acid drink low in tryptophan. A third group of abnormalities is sleep-related, specifically, persistent shortened rapid eye movement (REM) latency. Another group of abnormalities is neurocognitive. Particularly prominent are the dysfunctional attitudes and attributions that occur in depression and that have also been found to persist after symptomatic recovery.

The relation of these biological and neurocognitive abnormalities to residual symptoms has not been well studied, although they do appear to occur with full remission. Neither is there good evidence that they predict relapse, other than for dexamethasone suppression and REM sleep latency.

**Bipolar disorder**

This review primarily concerns unipolar disorder. However, there is a smaller but growing parallel literature regarding bipolar disorder. Two large prospective follow-up studies have found subthreshold symptoms present for substantial periods between episodes, as have a number of smaller earlier studies reviewed by Morriss, who also noted that these were most commonly residual after an episode.

Two recent studies found residual symptoms early after remission to be common. Keller et al had earlier described subsyndromal symptoms in about half of a sample of bipolar patients in a controlled trial of high- or low-dose maintenance lithium. Both of the large studies found these present for much longer than the periods of major disorder, and found that depressive symptoms predominated over hypomania. There has been less examination of the prediction of major relapses by these symptoms, but three studies found that, when present, these residual or inter-episode symptoms are strong predictors of relapse and recurrence.

**Conclusions:**

the nature and significance of residual symptoms

What can we say regarding the nature of residual symptoms in depression and their significance? There are various possibilities. Residual symptoms might represent persisting illness, the original illness continuing in milder form. Alternatively they might represent the phenomena preceding and underlying the depressive episode. Two possible aspects of the latter can substantially be discounted: subjects with residual symptoms are neither liable to be diagnosed as dysthymic nor, except to a minor degree, to show more personality abnormality than those who remit fully.

A third possible underlying phenomenon is that the residual symptoms could reflect the cognitive vulnerability of dysfunctional attitudes. However, the symptoms shown by residual depressives, although they include negative cognitions, are not limited to these, but include core mood and functional symptoms of depression. These are too wide to be related easily to a single abnormality of low self-esteem.

It thus seems likely, given these findings and the relative lack of association of residual symptoms with anything else except subsequent relapse, that the explanation is the first of those given above, persistence of the original disorder and its underlying neurobiological substrates. The most likely conclusion is that residual symptoms are a manifestation of a disorder that, in spite of improvement, is still present—they are evidence that the disorder continues. This is also supported by the tendency of relapses following residual symptoms to occur early. It reinforces the important practical treatment message: incomplete remission with residual symptoms indicates a high risk of relapse and a strong need for continuing treatment.

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**SYMPTÔMES RÉSIDUELS ET RECHUTE DANS LA DÉPRESSION**

Les symptômes résiduels, signe d’une rémission incomplète de la dépression, sont un important problème clinique. Ils surviennent chez environ un tiers des patients déprimés après un traitement aigu et ils englobent les symptômes typiques de la dépression à l’exception de ceux des troubles dépressifs majeurs. Leur conséquence la plus importante est une augmentation du risque de récidive, surtout la première année. Les symptômes résiduels sont révélateurs de la nécessité de poursuivre le traitement aigu pour davantage d’amélioration, si possible, de façon plus prolongée et à une posologie appropriée afin de prévenir une rechute. La thérapie cognitive est maintenant reconnue comme un traitement adjuvant efficace. D’autres anomalies persistantes sont retrouvées après une dépression comme l’inadaptation sociale, les comportements dysfonctionnels, l’hyperactivité de l’axe hypotalamo-hypophyso-surrénalien (HHS), le raccourcissement du temps de latence du sommeil paradoxal et la baisse de l’humeur après dépétition en tryptophane. On ne sait pas encore exactement jusqu’à quel point certaines de ces anomalies sont le reflet de symptômes résiduels ou des manifestations indépendantes, mais l’hyperactivité de l’axe HHS et le raccourcissement du temps de latence du sommeil paradoxal semblent bien être associés à l’augmentation du risque de récidive. Par ailleurs, on met de plus en plus en évidence l’existence de symptômes résiduels dans les troubles bipolaires, en particulier la dépression bipolaire, et leur présence témoigne également de l’augmentation du risque de récidive.
Is the patient really the same after a major depressive episode?

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Depression is a devastating disease for both the individual and his/her environment. The simple fact that someone suffers from depression constitutes a certain danger to the person in itself. The individual will experience bothersome symptoms such as lowered mood, loss of drive, anhedonia, pessimistic thoughts, overwhelming sadness, lack of perspective, low self-esteem, and many other symptoms, causing the patient's life to become unbearable and useless. Clearly, there is an impact on the patient's life and his/her family life. Therefore, depression is often considered as a disorder that affects the whole family. The most striking example may be the impact of a suicide attempt on family life. Thus, after a depressive episode, the patient himself, as well as the family, have experienced a very unpleasant mental condition that causes them to fear the next depressive episode. It is clear that everybody struggles to avoid the next episode or even the next hospitalization. The experience of a depressive episode seems also not to be neutral with regard to the patient's environment. Those who have survived depression may recognize a change in the attitudes of other people toward them; depressive patients may be considered by others as strange, different, unpredictable, or individuals of a lower vital potential. Studies have revealed that patients with depression experience stigmatization like that of patients with schizophrenia. Another problematic consequence of a depressive episode is of a purely biological nature. Several neurobiological mechanisms underlay the pathology of depressive symptoms (eg, neuroanatomical and neuroendocrine alterations, changes in neurotransmitter systems, etc). One can presume that sequential depressive episodes may cause the hypothetical biological background of depression to become even more severe, and each depressive episode may have a certain consequence for the brain as far as biological damage may be concerned. The nature of such consequences may include not only the real “toxic” influence of the biological factors that presumably constitute the basis of depression, but also the impact of the biological treatment. Biological therapy is a first-choice treatment for depression, but one needs to realize that such a treatment is under no condition free of any unfavorable impact on the functioning of the brain. The question indeed may be raised as to why we insist on treating depressive patients with predominantly biological methods, if the expected remission rates after pharmacological interventions in depression are only about 50% to 55%.5 The issue of a negative impact of treatment methods on the patient's brain should be given even more attention when dealing with patients who do not respond adequately to the treatment; the prevalence of “treatment-resistant” depression may constitute 50% of real-world patients. So-called “treatment-resistant patients” are usually subjected to numerous therapeutic attempts, and many such attempts are simply ineffective, necessitating introduction of the next treatment. Clinical experience tells us that such treatment-resistant patients are difficult to manage when the next depressive episode appears, because the previous treatment history causes both the patient and the clinician to develop treatment strategies that include more intensive methods of treatment (ie, higher doses, drug combinations, augmentation strategies, etc). Thus, in addition to biological treatment, psychosocial interventions (cognitive behavioral therapy, emotion-focused therapy, self-esteem therapy) should be recommended.

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Major depressive disorder (MDD) is a severe mood disorder characterized by single or recurrent major depressive episodes. A total of 50% to 85% of patients who have a depressive episode will eventually go on to have at least one other episode. Between 9% and 24% of patients with the initial diagnosis of a major depressive episode will undergo a change in diagnosis over time, mostly to bipolar disorder. Several risk factors have been identified for depressive relapse. The more episodes that an individual has, the more likely it is that another will occur. Other important risk factors include preexisting dysthymia, a family history of mood disorders, concurrent anxiety or substance abuse, and long duration of severe index episode. In recent years it has become apparent that the long-term course of unipolar MDD is not only characterized by high rates of recurrence, but also dominated by prolonged symptomatic chronicity. Many patients with MDD return to their premorbid level of functioning between episodes of major depression. However, in approximately 30% of severe or hospitalized depressed patients, residual symptoms and social or occupational impairment persists. Having residual symptoms or subsyndromal depression after acute treatment is also an important risk factor for relapse and recurrence. About one third of patients suffering from severe major depression with residual symptoms will have a chronic course marked by at least 2 years of illness. Epidemiologic and prospective clinical follow-up studies have also documented that the typical course of unipolar MDD involves fluctuating symptoms, whereby depressive subtypes included in official diagnostic systems do not represent discrete disorders, but are stages along a dimensional spectrum (continuum) of symptomatic severity. The group of chronic depressive disorders encompasses four subtypes of depressive illness: (i) MDD, recurrent, without full inter-episodic recovery (incomplete remission); (ii) MDD, currently in a chronic (duration of ≥2 years) episode (chronic MDD); (iii) dysthymic disorder; and (iv) “double depression” (concurrent dysthymic disorder and major depression). The group of “subthreshold depressions” (depressive disorders not otherwise specified) includes depressive conditions in which the number, duration, or quality of symptoms is insufficient to meet the Diagnostic and Statistical Manual of Mental Disorders criteria for a diagnosis of major depression. Patients with an early onset and older adults suffering an initial depressive episode after the age of 60 years appear to be at greater risk for the development of chronicity. Individuals suffering from either dysthymia alone or “double depression” have significantly greater impairment in functioning than those who present with major depression alone, depressive symptoms, or past episodes of major depression. Residual (subthreshold) symptoms in the course of MDD are associated with high risk of an early episode relapse and a significantly more chronic future course of illness. Recovery from MDD with full resolution of symptoms is associated with significant delays in episode relapse and recurrence, and a more benign course of illness. MDD is also associated with considerable morbidity and mortality, and for many, an initial episode of depression evolves into a debilitating chronic illness with significant and pervasive impairments in psychosocial functioning. Chronic depression is characterized by the increased utilization of health care services, reduced employment, and greater economic costs associated with affected individuals. Studies investigating the effects of depression on health-related quality of life demonstrate decrements that equal or exceed those of patients with chronic medical illnesses such as ischemic heart disease or diabetes mellitus. Patients who have experienced major depressive episodes are less likely to sustain a demanding job or career or to achieve full intellectual potential. If the first depressive episodes arise during adolescence or early adulthood, diminished performance at school or during vocational training or university is a frequent negative outcome with lifelong consequences. With the information given here, it becomes clear that the patient is not the same after he or she has suffered a major depressive episode, because of the persistent (high) risk of relapse and recurrence and development of a chronic course of subthreshold depression. Therefore it is important to note that one of the most important goals in clinical practice is to start with effective treatment early on, to achieve remission in the acute phase of treatment, and to attempt as much as possible to remove all residual depressive symptoms.

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CONTROVERSIAL QUESTION

3 • E. Sacchetti, Italy

The wide number of antidepressants currently available to clinicians constitutes a valuable opportunity for an improved management of patients with depression. Nevertheless, the short-term and long-term prognosis for the disorder remains persistently far from good in a relevant proportion of patients. Indeed, among depressed patients, at least one third inadequately responds to the first antidepressant, and approximately 1 out of 10 remains depressed even after multiple interventions. Furthermore, residual depressive symptoms are common in patients who respond to antidepressants. Finally, syndromal and subsyndromal continued depression cause persistent disability and impose a substantial socioeconomic burden. Since the possibility of a true restitutio ad integrum after depression is nowadays precluded in many patients, the acquisition of new antidepressants with improved efficacy-safety profiles and mechanisms of action that are able to work in otherwise refractory patients is certainly welcome. Treatment response represents indeed the final phenotypic result of pharmacokinetic and pharmacodynamic interactions that are both drug- and patient-specific, and are moderated by several other superimposed modifiable and unmodifiable characteristics of the patient, the health care system, wider society, and/or the environment in general. Two examples may suffice to support this paradigm: the first example pertains to poor treatment adherence, a well-known, widespread phenomenon that plays a key influential role in the outcome of depression, because it exposes the individuals to “false” poor responses, relapses, recurrences, and, with between-drug differences, withdrawal symptoms. The individual’s propensity to adhere to therapies for depression is defined by, along with other variables, cultural and attitudinal factors in general, social stigma about depression and its treatment, frequent facilitation by the media and resources in these areas of intervention in order to promote a widespread dissemination of these proactive strategies that are able to moderate modifiable modulators of treatment response.

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This is a very good question, with a very complex answer. From any angle that we examine this matter, it seems that the depressive experience changes the patient. The amount of information currently available on the neurobiological toxicity of depression is impressive. A simple search in PubMed using the key words “depression” and “brain derived neurotrophic factor (BDNF)” produces 517 articles, 89 of them published in the last 8 months, an example of the great interest that this topic arouses. The neurobiological approach, which is based mainly on the observation that patients undergo a decrease in BDNF and consequently neuronal atrophy and apoptosis—mostly of CA3 pyramidal hippocampus neurons—establishes the concept of depression-induced brain damage. This brain damage leads to functional consequences that, for example, predispose the individual to other depressive reactions when he is facing an adverse environment. Depression is also associated with increased activity of the hippocampus-hypothalamus-pituitary-adrenal (HHPA) axis, due essentially to a diminished amount and/or sensitivity of glucocorticoid receptors in the hippocampus. This adjustment of the axis can persist after a single depressive episode and can also predispose the individual to other depressive reactions when he is confronted by a stressful situation. To illustrate how a hyperfunctioning HHPA axis can prompt depressive episodes, we should remember that very early diminishment of maternal care can lead to promoter-region methylation of the glucocorticoid receptor gene in the hippocampus, leading to a reduction in the expression of this gene and hyperfunctioning of the HHPA axis, which is associated with post-stress depressive reactions. Furthermore, epigenetic modulation through methylation in the hippocampus is associated with suicide. In an alternative view, using epidemiological data, we can observe that the occurrence of one depressive episode predisposes the individual to another.

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More than a century ago, Emil Kraepelin divided the major psychoses into dementia praecox (schizophrenia) and manic-depressive illness, using longitudinal progression and prognosis as major, but not exclusive, dichotomizing concepts. Nevertheless, both Kraepelin and we know that some schizophrenics get well, and some manic depressives never will. The concept that depression and mania “always” in time will heal, has, however, become rooted in clinical practice. Modern research has nevertheless concluded that if chronicity is defined as never getting out of an episode, then perhaps 1 out of 10 afflicted patients will remain ill for more than 2 years. If chronicity is defined as ever recurring episodes, then half of patients with an episode of unipolar depression will experience another episode, and almost all bipolar patients will continue shifting between mood states if left untreated. So, affective patients get better, but have a propensity to remain to some extent symptomatic and to suffer recurring episodes. Is major depression, once it has had its debut, a state or a trait? There is certainly evidence for increasingly severe episodes: Robert Post developed the kindling or sensitization hypothesis of mood disorders in the 1980s, stating that episodes tend to accelerate over time and be increasingly independent of a triggering event, and the validity of this concept has been replicated. The heavy toll on personal suffering and society has been investigated. There is also evidence for neurobiological consequences of mood swings: mood disorders have been associated with neurodegenerative changes within the central nervous system—the best researched area being enlarged lateral ventricles and within the central nervous system—the best results of such studies to date have been the replicated demonstration that White carriers of two short arms in a polymorphism within the serotonin transporter gene are more susceptible to negative life events eliciting depressive episodes in adult life. In conclusion, if cerebral alterations in depression are viewed more as traits than states, then the line between mood disorders and, for example, schizophrenia would become blurred. Indeed, recently, genes have been found that are common to both bipolar disorder and schizophrenia. Few clinical psychiatrists, however, doubt that mood-stabilizing treatment helps. Most patients live almost comfortably with supportive medical and psychological help that hides their susceptibility to depression, making them resemble ordinary healthy individuals in tackling life’s vicissitudes.

Inflammation and oxidative stress within the central nervous system, not only with regard to dementia and the neurodegenerative disorders, but also the psychoses and mood disorders. Little is known about the temporal patterns of the central inflammatory process in patients with mood disorders. With regard to apoptotic cell death within the central nervous system, there is a large body of evidence for hippocampal neuronal apoptosis in depression and the importance of neurogenesis as a mechanism for the therapeutic effects of antidepressants and electroconvulsive treatment. The presence of neurogenesis as a mechanism for the therapeutic effects of antidepressants and electroconvulsive treatment. The presence of neurogenesis as a mechanism for the therapeutic effects of antidepressants and electroconvulsive treatment.

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Is the patient really the same after a major depressive episode?
Is the patient really the same after a major depressive episode? MEDICOGRAPHIA, VOL 31, No. 2, 2009

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Diverse adverse events such as separation, physical abuse, and traffic accidents can occur in everyone’s life and leave sequelae of variable intensity in many areas of human behavior. Major depressive disorder is a common but serious condition that causes distress to its victims, impairs family life, reduces social adjustment, and is a burden on the community. Depression is one of the most important public health problems in Korea: the prevalence of depressive disorders has increased 30% during the past 5 years according to a recent Korean national epidemiological study, and prescriptions of antidepressants have doubled in the last 5 years. In addition, the suicide rate in Korea is one of the highest among the Organization for Economic Co-operation and Development (OECD) countries. National depression initiatives from developed countries emphasize that awareness and recognition of depression is important, because depression is a treatable disease. There are many antidepressants that have proven efficacy and safety. However, the past two decades of research have shown that depression often runs a chronic, intermittent, lifelong course, although effective therapeutic approaches have been developed and provided. After acute episodes of illness, many patients do well for variable periods of time. However, more than half of patients have residual symptoms and impairment between episodes, despite ongoing therapy. Anxiety, sleep disturbance, somnolence/fatigue, apathy, and cognitive dysfunction are common residual symptoms and are associated with an increased risk of relapse and poor psychosocial functioning. Experience of major depressive episodes can lead to a change in psychological coping styles in patients. Many patients cope well with depression. They are able to escape negative thinking, and gain the capacity to be resilient. However, dynamic vulnerability theories suggest that consecutive depressive episodes cause biological and psychological changes that increase the vulnerability to subsequent depressive episodes. The experience of these episodes reduces the threshold for the individual's mind/brain to enter into the depressive state, such that episodes can occur with little or no environmental precipitant. Disabilities related to depression affect work, family, and social aspects of a patient's life. Many depressed patients choose to leave a job because of their depression and have difficulties in getting a new job. Due to the negative stigma related to depression, patients often choose not to disclose their condition at the workplace. Research shows that a significant proportion of men become depressed when their partners are depressed. There is an increase in marital conflict and discord within the families of depressed patients. Also, many patients with depression are unable to enjoy social and leisure activities. Alarmingly, many recovering depressive patients are often unaware of the long-term consequences of a maladaptive lifestyle, which include dysfunctional thought, chronic life stress, interpersonal friction, and inadequate rest. Major depressive episodes are believed to leave a substantial impact on many aspects of patients' lives for a long time, even after an acute episode has passed. Development and delivery of innovative psychotherapeutic, psychoeducational, and family therapeutic programs, as well as novel antidepressants, are essential for the recovery of depressed patients.

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The treatment of depression improves a variety of aspects of the illness, such as its symptoms, the patient's emotional well-being, and their occupational and social functioning. The conundrum as to whether the patient is really the same after a major depressive episode depends on whether remission or response is achieved. There are no biological markers for depression at present. Researchers in clinical trials utilize a 50% improvement on rating scales such as the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Åsberg Depression Rating Scale (MADRS) as a guideline for treatment response. Although HAM-D is recognized as the gold standard in clinical trials for depression, it has been shown that subscales on HAM-D outperform the total scale in this respect. The available rating scales do not assess or reflect optimal functioning. In clinical trials, one-third of patients achieve full remission, one-third achieve a response, and one-third are nonresponders. Research has shown that early remission improves long-term well-being, and patients treated to remission have fewer missed workdays. But there are various obstacles to attaining remission in clinical practice, such as noncompliance, treatment discontinuation due to side effects, and failure to recognize residual symptoms. Many responders may still have a substantial degree of residual or subthreshold symptoms, leading to clinically significant negative and unfavorable outcomes.\(^2\)\(^\text{2}\) Paykel et al. found that the rate of relapse in patients with a partial response was 76%, compared with 25% in patients achieving full remission.\(^1\) Even minimal levels of residual symptoms contribute to ongoing functional impairment and increase the risk of further depressive episodes to three to six times higher than in those with full remission. Additionally, treatment does not automatically improve social support outcomes. Residual symptoms are also associated with socioeconomic issues and help-seeking health care visits, chronicity, and the risk of suicidal thoughts and attempts.\(^2\) Unfortunately, whatever the improvement in mood symptoms, it is not synchronous with a full return of premorbid capabilities. Zimmerman et al. showed that for patients, psychosocial functioning is of great importance, and positive features such as “optimism, vigor, and self-confidence” were crucial in their own assessments of whether they had returned to their normal selves.\(^6\) Patients who were more likely to view themselves as being in remission reported significantly less psychosocial impairment, and better quality of life.\(^7\) Yet findings from studies indicate that treatment does not ensure immediate and complete recovery of all aspects of the patient’s life. A recent study found that feelings of hopefulness did not improve until several weeks or even months after depressive symptoms were controlled.\(^8\) In another study of primary care patients treated with selective serotonin reuptake inhibitors for major depression, symptoms continued to improve over time, while painful physical symptoms persisted.\(^9\) In addition, neurobiological investigations of brain perfusion have shown that there can be a delay in perfusion normalization for up to 2 years into remission, with increases in the frontal regions and decreases in the parietocerebellar regions.\(^10\) From the clinician’s perspective, despite the heterogeneity of the etiologic mechanisms underlying depression such as the genetic antecedents, early trauma, and stress, and the various psychosocial factors such as coping styles, interpersonal events, and parental bonding experiences, which can impact recovery, the aim is to have very clear treatment goals for each patient, with detailed assessments and monitoring. Attention should be paid to underlying personality factors, comorbid psychiatric conditions, and co-existing medical conditions. The aim is for complete remission, not only through pharmacotherapy, but also a more holistic approach with the use of psychotherapeutic treatments and social interventions.\(^2\)\(^\text{3}\)

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Both biological and psychological factors are believed to play a role in the development of major depressive disorder (MDD). While the tendency to develop depression may be inherited or triggered by environmental stressors such as stressful life events, the traditional view is that depressive symptoms are a consequence of an imbalance in the neurotransmitters within the central nervous system; namely, norepinephrine, serotonin, and dopamine, which are involved in the regulation of mood and emotion. It is well known that the risk of recurrence increases with each subsequent episode of depression. While the onset of depressive episodes becomes easily triggered over time, it is progressively less associated with environmental stressors. This phenomenon supports the “kindling hypothesis,” which proposes that psychosocial stressors play a greater role in the initial than in subsequent episodes of depressive disorders. Kendler and colleagues, in their study of white female-female twin pairs, further documented a threshold of approximately 9 episodes of depression at which the brain is no longer additionally sensitized to the depressive state. Their evidence suggests some neurobiological and neuroanatomical alterations that occur intensely in the brain during depression, even during the first few episodes of illness. Chronic activation of the stress-response system in MDD can cause a variety of adverse effects in the brain, and mediates many of the physiological and behavioral responses in depression. For example, an elevated level of corticotropin-releasing factor in depression is found to mediate some of the behavioral symptoms of depression involving sleep and appetite disturbances, reduced libido, and psychomotor changes. Current evidence has also shown the involvement of neurogenesis in depression, though its role has not been clearly elucidated yet. Neuronal atrophy and cell death occur as a result of hyperactivity of the stress-response system, in which adrenal glucocorticoid release is increased, while brain derived neurotrophic factor (BDNF) levels decline. More recent research suggests an association between depression and neurogenesis of the hippocampus, a structure essential to learning and memory, contextual fear conditioning, and neuroendocrine regulation. The damaging effects of prolonged stress could contribute to the selective loss of hippocampal volume. A number of neuroimaging studies have unanimously shown that patients with recurrent and/or severe depression tend to have smaller hippocampal volumes. These morphological changes were noted to persist long after depressive symptoms had resolved. Hippocampal volume reduction is also found to be greater in patients who have had a longer duration of illness and who went untreated, indicating that prolonged depression may result in progressive and cumulative damage to the brain. All these findings underscore the urgency for aggressive treatment early in the course of illness to achieve remission and to prevent a chronic, recurrent depressive course. It was demonstrated during a 2-year follow-up study that treatment to the point of symptom remission in the first 3 months significantly decreased the risk of relapse and recurrence. The therapeutic effects of antidepressants are believed to be the result of the drugs’ abilities to restore neurotransmitter imbalance at the synapses. However, most antidepressants appear to have a delayed onset of action. An experimental animal model study found that the onset of therapeutic effects following the initiation of antidepressant treatment neither coincides with the achievement of therapeutic serum concentrations nor with the inhibition of neurotransmitters. This raises questions about the traditional “chemical imbalance” hypotheses regarding the underlying pathophysiology of depression. Additionally, despite the fact that depression is traditionally viewed as a fully reversible disorder, accumulating evidence suggests otherwise. More recent evidence indicates that beyond restoring the chemical balance at the synapses, antidepressants may have effects associated with re-establishment of neurobiological activity in the brain. For example, antidepressant pharmacotherapy affects serotonin and/or norepinephrine activities, thereby affecting neuronal survival and growth by decreasing glucocorticoid levels and increasing BDNF levels. In fact, Malberg and colleagues have shown that chronic antidepressant treatment was able to increase neurogenesis in the adult rat hippocampus. In human subjects, it has been reported that patients with mood disorders who were receiving an antidepressant at their time of death, had greater hippocampal BDNF expression compared with untreated subjects. In essence, patients are unlikely to be the same after a major depressive episode, as neurobiological and neuroanatomical changes have taken place in the brain. Early and aggressive antidepressant therapy is hence imperative to achieve remission and prevent recurrence in the long term.

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Is the patient really the same after a major depressive episode?

The spontaneous and first answer to this question should be a clear “no!”, as any significant experience in life—and a major depressive episode undoubtedly is—has the effect of modifying the subject’s global perspective about himself and the world. This can be appraised through the vast literature produced on the matter, one such recent example being W. Styron’s first person account. But this answer probably fails to respond to the implicit insinuation that after having recovered from a major depressive episode, the patient has somehow permanently deteriorated in his functioning (what is known as the “scarring” effect of depression), and what may be a consequence of that is a high risk of subsequent episodes. It is well documented that depression frequently has a chronic course with recurrences and that the probability of presenting with a new episode increases with the number of previous ones. There are also numerous studies showing that individuals with a history of depressive episodes have higher scores in some pathological personality characteristics, such as interpersonal dependency, lack of social confidence, submissiveness, neuroticism or introversion. The role of these characteristics as being only state markers or acting as vulnerability factors has been largely discussed; but a third possibility has emerged that at least some of them could be a consequence of the depressive episode, thus producing a kind of “scar,” a relatively permanent residual deficit (by analogy with physical scars after an injury). This is known as the “scar hypothesis” of depression, which has been introduced as such in the early 1980s. Since then, there has been wide controversy around this possibility, with most published work on the issue showing results that did not support the scar hypothesis (it is possible to show them “in extenso,” but a representative sample may be Rohde et al., Shea et al., Ormel et al., and Kennedy et al. Taken as a whole, they indicate that postdepressive vulnerabilities correspond to the continuation of premorbid conditions. Nevertheless, some findings are still interpreted as being residual impairments—mostly in the realm of emotional reactivity—that last longer than the remission of symptoms and may even become “latent,” so as to mean that they would not appear except in emotionally charged situations. Almost in parallel to that, increasing attention has been devoted to the problem of residual symptoms after a depressive episode, a phenomenon whose clinical relevance relates to the dysfunction it can cause and also the risk of relapse that is significantly increased by its presence. In this case we will be facing a “badly cured” episode instead of a permanent scar, with “unresolved symptoms” that may be under the threshold of clinical diagnosis, but have a relevance that needs more detailed study. The prevalence and mechanisms involved in these subthreshold conditions are not well known, but they may force us to review some of the concepts involved (remission, recovery, euthymia), as well as the difficulty in making prognostic and therapeutic decisions based upon a diagnostic category so heterogeneous as “major depression,” something that has already been pointed out. After more than 50 years of using antidepressant agents, we are still facing the complexities of the nosology of depression, as it requires an adequate coverage of a variety of different clinical presentations in terms of severity and chronicity. Going back to the initial question, it seems very clear that a major depressive episode will probably change the patient (although not necessarily for the bad if well treated) but an additional point should also be that we have to review our standards of treatment, looking for a more ambitious target and not merely remission of symptoms below the level of diagnosis. If we achieve that, patients will have a better chance of regaining a level of functioning that is at least as good as they previously had.
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Major depressive illness is a chronic relapsing condition that sometimes warrants lifetime treatment. Studies on the long-term outcome of major depression have shown a significant difference between unipolar and bipolar types. More confusion is added when unipolar depression switches to bipolarity in later years, thus affecting the results of long-term outcome studies.1 Furthermore, the classification and diagnosis of depression is in effect that of a cluster or set of symptoms, or a syndrome. We therefore treat these symptoms, and not a diagnosis as such.2 Thus response and quality of life is measured by the response of these symptoms to treatment. The diagnostic categories of major depression and the presence of comorbidities affect the results of studies on the long-term outcome of depressive illness. Antidepressants have grown in number, as have their different mechanisms of action and molecular types. They all show varying degrees of ability to generate a response in comparison with placebo. Furthermore, short-term studies show that all antidepressants have a low advantage over placebo (15%-20%) i.e., 50% of depressed patients improve on placebo, although we are unable to know which patients do well on placebo.3 The duration of depression treatment in clinical practice varies, even though treatment algorithms do exist, and Isomesta et al4 showed that about 70% of patients receive subtherapeutic doses of antidepressant. Randomized controlled trials by Schulberg et al5 and Katon et al6 showed that adequate treatment according to the US Agency for Health Care Policy and Research guidelines gives a clinical outcome that is superior to that of usual treatment. Gender and the response to antidepressants has also been studied, and has shown that tricyclic antidepressants are more effective in males and that selective serotonin reuptake inhibitors are more effective in females.7 Compliance is difficult to study, and is a problem that is not resolved in assessing outcome.8 Last but not least, cure is a relative term whose definition varies from symptom relief, to social recovery, adaptive behavior, and remission. It is infrequently the case that a patient is cured of depression, in the sense that no further attacks of depression occur in the lifespan of the patient, and this is even less frequent with bipolar depression. Against the backdrop of all the above intricacies, controversies, and clinical variations, there is increasing literature on the unsatisfactory degree of remission achieved with current treatments in depression. A Medline review of relevant articles published from 1967 to 2006 showed that when psychotherapy and pharmacotherapy are used to treat depression, most patients report residual symptoms despite apparently successful treatment. These residual symptoms have strong prognostic value, as they have a relationship with prodromal symptoms that can lead to relapse.9 This subject has received inadequate attention. Review of the literature using Medline also showed that some clinical findings point toward: (i) unfavorable long-term outcomes in depression treated by available antidepressants...
(paradoxical depression-inducing effects), with anxiety and depressive symptoms; (ii) antidepressant-induced switching and cycle acceleration in bipolar disorders; (iii) occurrence of a tolerance to antidepressants in long-term treatment; and (ii) withdrawal effects after stopping treatment, with possible relapse. Residual symptoms are the rule in unipolar depression. The symptoms are related to the hypothalamic-pituitary-adrenal axis and to sleep architecture, and are predictors of relapse, as they progress to become prodromal symptoms of relapse upon recovery from the depressive episode. So antidepressants should not only be assessed on their differential remission rates, but also on the differential amount of residual symptomatology after response. Treatment of these residual symptoms may improve long-term outcome, so that recovery lies not exclusively in the alleviation of the negative, but also in engendering the positive. The above discussion focuses mainly on unipolar depression, in which there is growing controversy about the concept of “total cure.” The situation is no better in bipolar depression, where the spectrum of patients runs the full range from highly functional, well-adjusted individuals who are almost completely symptom-free for decades, to socially dysfunctional, chronically ill patients with repeated relapses, who never recover. In general, in bipolar illness, depression has a more chronic natural course than the mania, with patients reporting chronic subsyndromal depression. In conclusion, unipolar depression, a chronic and relapsing illness, sometimes runs a course that is without full recovery, full recovery being a term that can be confused with remission or social recovery, meaning the patient is never really the same after a major depressive episode. There is more controversy with regard to bipolar depression, where it sometimes takes over 10 years for a diagnosis to be made, and where the progress toward recovery is often poor, with no remitting cyclical course.

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BETTER QUALITY REMISSION IN DEPRESSION: VALDOXAN, THE FIRST MELATONERGIC ANTIDEPRESSANT  

by C. Muñoz, France

Despite all the treatments developed in recent years, depression remains a disabling illness. Existing antidepressants have mixed clinical benefits and side effect profiles that often impair quality of life. It was initially hoped that selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) would circumvent the disadvantages of tricyclic antidepressants (TCAs) and selective or non-selective monoamine oxidase inhibitors (MAOIs). The reality is that although SSRIs and/or SNRIs and other dual action antidepressants are better tolerated, they still have undesirable side effects. Sexual dysfunction, gastrointestinal upsets, weight gain, antidepressant discontinuation syndrome, and sleep disturbance are only not decrease and, in some cases, destroy adherence, they also prevent complete remission. Indeed, complete and sustained remission has become the main goal in treating major depressive disorder (MDD). Incomplete remission is viewed as treatment failure, with residual symptoms being a predictor of relapse and recurrence. Therefore the need for novel pharmacologic entities that can offer relief from the illness together with a significant reduction in residual symptoms. Candidates have, for example, included receptor antagonists to neurokinin 1 (NK1) and corticotropin releasing factor (CRF). However, neither class offered consistently positive results in clinical trials and both also act, albeit indirectly, via monoaminergic mechanisms.

A more innovative and promising strategy is to base antidepressant therapy on the regulation of circadian rhythms. The rationale that resulted in the synthesis of Valdoxan (agomelatine S 20098) is based on the observation that circadian rhythms are disturbed in depressed patients and that abnormal rhythms play a key role in depressive episode outcome. Valdoxan is the first melatonergic antidepressant. Its binding profile differs from that of all other antidepressants. Valdoxan is a potent melatonergic MT1 and MT2 receptor agonist and a serotonergic 5HT2C receptor antagonist. As such, it represents a novel pharmacologic approach to the treatment of MDD.

This review highlights the innovation represented by this mechanism of action, summarizes the drug’s preclinical and clinical properties, and identifies the features that enable this fresh approach to the treatment of depression to ensure a better quality of remission.

Pharmacologic properties of Valdoxan: a truly innovative antidepressant therapy

◆ Receptor profile
Valdoxan binds strongly to cloned human MT1 and MT2 receptors with affinity (Ki) values of 0.10 ±0.1 nM and 0.12 ±0.02 nM. Its estimated Ki for 5HT2C

Good quality remission is rarely achieved with conventional antidepressants, suggesting that targets other than the monoaminergic system hold the key to effective drug therapy. A novel example is circadian rhythm regulation, based on the finding that circadian rhythms are disturbed in depressed patients and that such disturbance is an important factor in depressive episode outcome. Valdoxan (agomelatine) is the first melatonergic antidepressant. As the first antidepressant to be an agonist at melatonergic MT1 and MT2 receptors and an antagonist at serotonergic 5HT2C receptors, it has a unique receptor profile for regulating disturbed circadian rhythms. It has demonstrated antidepressant efficacy against placebo in the short and long term, irrespective of disease severity, and has also outperformed venlafaxine and sertraline on several rating scales, especially those reflecting clinical practice. Efficacy is associated with unique clinical benefits such as non-sedative regulation of the sleep-wake cycle and improved daytime functioning as early as the first treatment week. Valdoxan does not depress libido or sexual function, nor induce antidepressant discontinuation syndrome or weight gain, and it is well tolerated. These features make it a truly novel approach to depression, providing early symptomatic relief within a framework of complete and sustained remission.

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Keywords: internal clock; circadian rhythm; unique receptor profile; antidepressant efficacy; remission; discontinuation syndrome; sexual function; body weight; Valdoxan (agomelatine)

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Valdoxan is an agonist at melatonergic MT1/MT2 receptors and an antagonist at 5HT2C receptors. Its affinity for other receptors or transporter sites is negligible. IC50, inhibitory concentration–50.

Valdoxan has proven efficacy in animal models of depression. Valdoxan (10–50 mg/kg per os [PO] or IP) has shown antidepressant efficacy in a comprehensive and validated battery of animal models; despair test, olfactory bulbectomy, transgenic mice with glucocorticoid receptor deficiency, unavoidable aversive light stimulus, learned helplessness, and chronic mild stress. In the latter model, a melatonergic agonist abolishes the antidepressant effect observed in the evening but not that observed in the morning, clearly showing that the antidepressant efficacy of Valdoxan requires both melatonergic and 5HT2C receptors.

**Resynchronization of circadian rhythms**

Valdoxan demonstrates efficacy in all animal models of depression

Valdoxan (10-50 mg/kg per os [PO] or IP) has shown antidepressant efficacy in a comprehensive and validated battery of animal models; despair test, olfactory bulbectomy, transgenic mice with glucocorticoid receptor deficiency, unavoidable aversive light stimulus, learned helplessness, and chronic mild stress. In the latter model, a melatonergic agonist abolishes the antidepressant effect observed in the evening but not that observed in the morning, clearly showing that the antidepressant efficacy of Valdoxan requires both melatonergic and 5HT2C receptors.

**Other activities**

Single dosing with Valdoxan (10–40 mg/kg IP) has proven anxiolytic activity in the elevated plus maze, social defeat model, Geller-Seifert and Vogel conflict tests, and social interaction tests. 5HT2C antagonists are effective in these models and melatonin antagonists have no effect. The preclinical studies show that this efficacy is dependent on both melatonergic receptor agonism and 5HT2C receptor antagonism. No other increase in dopamine has been observed in other brain areas, specifically nucleus accumbens or striatum.

**Resynchronization of circadian rhythms**

**Resynchronization in models of circadian rhythm disturbance**

In rats, single or repeated dosing with Valdoxan (5–10 mg/kg PO) resynchronizes locomotor activity in models of jet lag, blindness, and delayed-phase sleep; it also resynchronizes circadian rhythms in two therapeutic models: aging and trypanosome infection.

**Resynchronization of circadian rhythms in an animal model of depression**

In a naturalistic and well-validated animal model of depression (the subdominant tree shrew), Valdoxan (40 mg/kg PO) resynchronizes body temperature, while restoring body weight and urinary cortisol. Melatonin and 5HT2C antagonists have no effect in the same model.

**Resynchronization of circadian rhythms in healthy volunteers**

In healthy volunteers, chronic exposure to a therapeutic dose of Valdoxan (50 mg) induced an approximate 2-hour phase advance of body temperature and cortisol rhythm and an increase in plasma growth hormone. No effect on polysomnography variables is observed. These results are reinforced by the impact of Valdoxan in depressed patients (see next section: Clinical studies).

**Mechanism of action: a novel approach to depression**

Valdoxan has proven efficacy in animal models of depression in which melatonin and 5HT2C receptor antagonists have no effect. The preclinical studies show that this efficacy is dependent on both melatonergic receptor agonism and 5HT2C receptor antagonism.
The results suggest that neither the affinity for either receptor alone nor a simple combination of the two pharmacologic activities suffice to provide antidepressant activity. The receptors could therefore be acting in synergy (rather than in combination) to achieve antidepressant efficacy via complete regulation of circadian rhythms. Several lines of evidence substantiate this proposed mode of action: (i) high MT1, MT2, and 5HT2C receptor density in the suprachiasmatic nucleus and hippocampus; (ii) involvement of all these receptors in the regulation of circadian rhythm; (iii) circadian expression of MT1 and 5HT2C receptors; and (iv) beneficial effects on sleep by melatonergic agonists and slow-wave sleep promotion by 5HT2C receptor antagonists.

This mechanism of action represents a true innovation in antidepressant therapy.

**Clinical studies:** Valdoxan is a potent antidepressant, providing faster, fuller, and more sustained relief

Three short-term pivotal studies have demonstrated antidepressant efficacy versus placebo, while comprehensive evaluations have shown that this efficacy is sustained across all grades of depression. Efficacy has also been evaluated in head-to-head comparisons versus venlafaxine and sertraline.

* Superior efficacy to placebo: short-term studies
  * Dose-ranging study
    This was an international, double-blind, randomized, phase 2, parallel-group efficacy study over 8 weeks in 711 patients with MDD (including bipolar II disorder) of Valdoxan 1-5 mg or 25 mg given in the evening versus placebo using paroxetine 20 mg as the internal comparator. The efficacy end point (mean decrease in total score on the 17-item Hamilton Rating Scale for Depression [HAM-D17]) confirmed the efficacy of Valdoxan 25 mg versus placebo (Δ2.57; P=0.034), as did the secondary end points: Montgomery-Asberg Depression Rating Scale (MADRS; P=0.016), Clinical Global Impression–Severity (CGI-S) scale (P=0.049), number of responders (61.5% vs 46.3%; P=0.036), and time to first response (P=0.008).

* Flexible dose studies
  Two international, double-blind, randomized, parallel-group studies confirmed the antidepressant efficacy of Valdoxan 25 mg versus placebo over 6 weeks. The dose could be increased up to 50 mg if improvement was insufficient (based on pre-determined cut-offs on the HAM-D17 and CGI scales) after 2 weeks. The design was unique in that it was performed via an interactive voice system. In both studies (n=2338 and n=2129), Valdoxan was more effective than placebo in terms of the mean HAM-D score in both the total population (Δ=3.44; P<0.001 [Figure 2]) and Δ=2.3; P=0.026) and dose-adjusted population (Δ=3.71; P=0.018 and Δ=3.13; P=0.045). Secondary end points showed improvement with Valdoxan in CGI-S score, number of responders, and time to first response survival analysis.

* Efficacy in severe depression
  In all three placebo-controlled pivotal studies, Valdoxan showed significant efficacy in the severe subpopulation, irrespective of the severity criteria used (baseline HAM-D score ≥25 or HAM-D score ≥25 and CGI score ≥5). Meta-analysis of the pooled study data (296 patients randomized to Valdoxan and 295 to placebo) showed that when the population was divided into subgroups using increasing cut-off HAM-D scores (stepwise from HAM-D ≥24 to HAM-D ≥30) at inclusion, antidepressant efficacy persisted irrespective of baseline severity (Δ=2.06; P=0.021 and Δ=4.45; P=0.025 for HAM-D cut-offs of 22-25 and >30) (Figure 3).

* Superior efficacy to placebo: long-term studies
  A relapse prevention study randomized responders to Valdoxan 25-50 mg after 8-10 weeks to continue

Figure 2. Mean Hamilton Rating Scale for Depression (HAM-D) total scores (adjusted for center and baseline; last observation carried forward) in the Valdoxan (25-50 mg) and placebo groups of a randomized, double-blind, parallel group trial. *P<0.05; **P<0.01; ***P<0.001.


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Figure 3. Pooled results of positive placebo-controlled studies on Valdoxan showing antidepressant efficacy in severely depressed patients. Hamilton Rating Scale for Depression (HAM-D) difference from placebo (6-8 weeks; last observation carried forward). The efficacy of Valdoxan 25-50 mg is maintained whatever the degree of severity at inclusion.


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Valdoxan or placebo for 6 months (or an optional 10 months). The differences in cumulative relapse rates (21.7% vs 46.6% and 23.9% vs 50%) at both 6 and 10 months, respectively, were highly significant: \( P < 0.0001 \), with nearly 8 in 10 patients relapse-free on Valdoxan, and a risk of relapse half that of placebo. The effect was confirmed in the severely depressed subpopulation.

**Efficacy versus venlafaxine and sertraline: short-term and long-term studies**

A head-to-head comparative study randomized patients to Valdoxan 25-50 mg (n=163) and venlafaxine 75-150 mg (n=165) in a flexible dose design for 6 weeks extending up to 6 months. Improvement on the CGI-improvement (CGI-I) scale was much greater as early as the first week in the Valdoxan patients (\( \Delta = 0.39 \); 95% confidence interval [CI], 0.20-0.58; \( P < 0.0001 \)) and remained so at both 6 weeks (\( \Delta = 0.32 \); 95% CI, 0.06-0.58; \( P = 0.016 \)) and 6 months (\( \Delta = 0.32 \); 95% CI, 0.04-0.6; \( P = 0.025 \)).

Another head-to-head comparative study randomized patients to Valdoxan 25-50 mg (n=150) and sertraline 50-100 mg (n=157) for 6 weeks up to 6 months. The response rate was significantly higher with Valdoxan at week 2 (20% vs 10.9%; \( P = 0.027 \)), and at 6 weeks, the scores on the three assessment scales were significantly superior—HAM-D (\( \Delta = 1.68 \); \( P = 0.031 \)), CGI-I (\( \Delta = 0.29 \); \( P = 0.023 \)), and CGI-S (\( \Delta = 0.28 \); \( P = 0.043 \)). At 6 months, the response rate was significantly higher with Valdoxan (76% vs 63.5%; \( P = 0.017 \)).

**Anxiolytic activity**

Valdoxan is not only an effective antidepressant, it also relieves the associated anxiety, as shown using the Hamilton Anxiety Scale (HAMA) in a dose-ranging study versus placebo (\( \Delta = 3.43 \); \( P = 0.011 \)), and in the meta-analysis of positive placebo-controlled studies in which Valdoxan patients scored significantly better versus placebo in the psychic and somatic anxiety items (items 10 & 11) of the HAM-D scale, including patients not on concomitant benzodiazepines. Valdoxan also outperformed sertraline in terms of HAMA scores at 6 weeks (\( \Delta = 2.36 \); 95% CI, 0.45-4.26; \( P = 0.016 \)).

**Better quality remission with Valdoxan**

Underlying the antidepressant efficacy of Valdoxan is a property not shared by any other available treatment: regulation of the sleep-wake rhythm, which complements and enhances a number of equally unique clinical benefits ensuring better quality remission. Sedation, daytime somnolence, sexual dysfunction, antidepressant discontinuation syndrome, and weight gain are all remarkable by their absence on Valdoxan therapy, contributing to excellent overall tolerability.

**Regulation of the sleep-wake rhythm: unique to Valdoxan**

As expected from its pharmacological profile, Valdoxan restores the disturbed sleep-wake rhythm, which is one of the earliest and most disabling aspects of depression. Valdoxan also eliminates daytime drowsiness. Two studies have evaluated the effect of Valdoxan on sleep-wake patterns using objective measures (polysomnography) and subjective questionnaires. Other information has come from subanalysis of the HAM-D sleep items in the pivotal studies.

**Objective studies**

In the first study, depressed patients received Valdoxan 25 mg in the evening for 42 days under open conditions with regular polysomnography. The results showed increased sleep efficiency (\( P = 0.05 \)), decreased intrasleep awakenings (\( P = 0.041 \)), increased slow-wave sleep (stages 3 and 4) both absolutely (\( P = 0.037 \)) and relative to the total sleep time (\( P = 0.022 \)), absence of change in total rapid eye movement sleep, and gradual improvement in the delta sleep ratio. Redistribution of slow-wave sleep through the night normalized sleep architecture.

The head-to-head comparison versus sertraline used actimetry to demonstrate improvement by the end of week 1 on Valdoxan in the objective sleep-wake parameters sleep efficiency, sleep latency, and sleep-wake time.

**Subjective studies**

A 6-week randomized double-blind study compared the effect of Valdoxan 25-50 mg and venlafaxine 75-150 mg on subjective sleep quality and integrity of behavior using the Leeds Sleep Evaluation Questionnaire (LSEQ) and Visual Analog Scale (VAS).

![Figure 4. Effects of Valdoxan 25-50 mg and venlafaxine 75-150 mg after 1 week of treatment on the first item in the Leeds Sleep Evaluation Questionnaire (LSEQ; “ease of getting to sleep”, left panel) and on daytime functioning (Visual Analog Scale [VAS]; right panel). Valdoxan regulates sleep better than venlafaxine with improvement in patients’ daytime condition from the first week of treatment. Based on data from reference 38.](image-url)

It showed significantly greater improvement with Valdoxan in the LSEQ items “getting to sleep” (\( P = 0.007 \)) and “quality of sleep” (\( P = 0.015 \)) in week 1. This effect persisted until the end of treatment. Significantly greater improvement was also noted in “daytime alertness” and “sensation of well-being” (\( P = 0.001 \) in week 1), indicating earlier improvement of daytime functioning (Figure 4). The study versus sertraline replicated these findings, showing earlier improvement in “getting to sleep” (\( P = 0.01 \)) and “quality of sleep” (\( P = 0.025 \)) with Valdoxan as early as week 1.
Valdoxan improves sleep through the night: effect on early and middle insomnia and early awakening

In the subanalysis of the three pivotal efficacy studies, Valdoxan 25-50 mg was significantly better than placebo on HAM-D sleep subscales in all three phases of sleep: early insomnia (P<0.001), middle insomnia (P=0.015), and early awakening (P=0.006). The difference versus placebo remained significant even without the HAM-D sleep items.41

Preservation of sexual functioning

There has been no evidence at any time in its development that Valdoxan impairs sexual function. Sexual emergent adverse events were few and similar on Valdoxan and placebo. A 12-week specific study versus venlafaxine using the Sex Effects Scale in 276 depressive patients, of whom 193 were sexually active at baseline, showed higher scores for pre-orgasm and orgasm with Valdoxan 50 mg than with venlafaxine 150 mg; the same was true in patients who achieved remission (n=111).44 A study in 92 healthy male volunteers randomized to Valdoxan (25 or 50 mg), paroxetine 20 mg, or placebo for 8 weeks confirmed the nil-effect on sexual function using the Psychotropic-Related Sexual Dysfunction-Salamanca Sex Questionnaire (PRSEX-DQ-SALSEX). Sexual dysfunction was significantly more gastrointestinal TEAEs than those receiving paroxetine 20 mg reported significantly more gastrointestinal TEAEs than those on placebo (P<0.001) (Table I). Comparison versus sertraline 50-100 mg showed fewer TEAEs caus-

Absence of the discontinuation syndrome

Abrupt discontinuation of conventional antidepressant treatment can trigger some very disturbing symptoms that typically last several days and include nausea, delirium, chills, and sleep disturbance. This does not occur with Valdoxan. A randomized, double-blind and placebo-controlled study explored the possibility of discontinuation syndrome with Valdoxan versus paroxetine as the active control. In stable MDD remitters, abrupt cessation of the 12-week treatment with Valdoxan 25 mg induced no symptoms on the Discontinuation Emergent Signs and Symptoms (DESS) checklist after 1 week. Abrupt replacement of paroxetine by placebo, on the other hand, induced many more emergent symptoms than in patients remaining on paroxetine (P<0.001).46

Superior tolerability to conventional antidepressants

Tolerated as well as placebo, including with respect to body weight

In the short-term studies, the percentages of patients reporting at least one treatment-emergent adverse event (TEAE) on Valdoxan were low and similar to placebo, as were the overall rates of TEAEs and their nature. The most frequent adverse events reported in both groups were headache, nausea, and fatigue.44 No clinical relevant changes in body weight (Figure 5) were observed on Valdoxan 25-50 mg. Most TEAEs occurred in the first 2 weeks of treatment and were mild to moderate, transient, and self-resolving. Rates of dropout due to adverse events were similar for Valdoxan 25 mg (5.5%), Valdoxan 50 mg (5.2%), and placebo (5.2%).

Valdoxan has a cardiovascular safety profile similar to that of placebo. Hematology and clinical chemistry show nil of note. There have been cases of liver enzyme elevation (1.1%; without clinical signs and reversible). Valdoxan has no apparent effect on hormone levels, including prolactin.

Superior tolerability to venlafaxine, paroxetine, and sertraline

The safety profile of Valdoxan 25-50 mg compared favorably with venlafaxine 75-150 mg over treatment for 6 or 12 weeks.43 Fewer patients withdrew due to TEAEs on Valdoxan (4.2% vs 13.2% and 2.2% vs 8.6% after 6 and 12 weeks). There were also fewer total TEAEs, in particular gastrointestinal disturbances and dizziness, on Valdoxan. An 8-week dose-ranging study12 showed no difference in tolerability between Valdoxan 25 mg and placebo, whereas patients receiving paroxetine 20 mg reported significantly more gastrointestinal TEAEs than those on placebo (P<0.05) (Table I). Comparison versus sertraline 50-100 mg showed fewer TEAEs caus-

<table>
<thead>
<tr>
<th>Patients reporting emergent adverse events (%)</th>
<th>Valdoxan (25 mg/day)</th>
<th>Placebo</th>
<th>Paroxetine (20 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6.6</td>
<td>8.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.6</td>
<td>3.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.6</td>
<td>3.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.6</td>
<td>2.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>4.3</td>
<td>17.0*</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.9</td>
<td>5.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Depression</td>
<td>2.9</td>
<td>2.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.9</td>
<td>2.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Table I. Main emergent adverse events (% patients in the safety set) reported by at least 3.5% of patients in any treatment group. Data from all patients who received at least one dose of treatment (even without efficacy evaluation). *P<0.05 (compared with placebo).

anxiety. Vascular effects and does not cause panic attacks or like TCAs, mirtazapine, and SNRIs), it has no cardio-gic receptors or norepinephrine transporters (un-

Because Valdoxan has no affinity for muscarinic receptors (unlike TCAs), it does not cause dry mouth, somnolence, blurred vision, urinary retention, or memory deficit.

Because Valdoxan has no affinity for histamine receptors (unlike TCAs and mirtazapine), it does not cause sedation or weight gain.

Because Valdoxan has no affinity for noradrener-gic receptors or norepinephrine transporters (un-

Valdoxan: superior treatment adherence

Proven short-term and long-term efficacy combines with these unique clinical benefits to generate bet-
ter treatment adherence than with the active compar-
ators used in the specific studies. Meta-analysis of the two head-to-head studies showed that more patients continued treatment with Valdoxane beyond 6 months than with venlafaxine and sertraline (69.4% vs 61.5%; P<0.05).

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Conclusions

As the first melatoninergic antidepressant, Valdoxan is also the first new pharmacologic approach to depression since the SSRIs. Its novel mode of ac-

tion has been shown to answer most of the unmet needs in depression therapy. By restoring bio-

logical rhythms, Valdoxan acts at the very core of depression, providing potent short- and long-term ef-

ficacy, exemplified in severely depressed patients, and outperforming the standard therapeutic op-

tions in this regard, namely SSRIs and SNRIs. The regulation of sleep-wake rhythms enables Valdoxan to relieve the disturbed sleep experienced by de-

pressed patients, and to do so uniquely—not only without sedation or a hangover effect but with in-

increased daytime alertness and preserved daily ac-

tivities, all from the very first treatment week.

This novel mode of action also accounts for the favorable side-effect profile of Valdoxan. The striking absence of weight gain, sexual dysfunction, and dis-

continuation syndrome helps to secure unmatched levels of treatment adherence.

Conventional treatments achieve remission in only a third of depressed patients. Even then the remission is often of poor quality due to residual symptoms. Its properties make Valdoxan unique in the antidepressant armamentarium. It improves quality of life during treatment and achieves bet-

ter quality remission by acting directly on residual symptoms. As such, Valdoxan may well represent the antidepressant medication that patients and the psychiatric community have been waiting for. }

Better quality remission in depression: Valdoxan, the first melatonergic antidepressant – Muñoz

AMÉLIORER LA QUALITÉ DE LA RÉMISSION DANS LA DÉPRESSION : VALDOXAN, LE PREMIER ANTIDÉPRESSEUR MÉLATONINERGIQUE

L e fait que les antidépresseurs classiques confèrent rarement une rémission de bonne qualité suggère que d’autres modèles que le système monoaminergique pourraient ouvrir la voie à un traitement efficace. La régulation des rythmes circadiens en est l’illustration, fondée sur la perturbation de ces rythmes chez les patients déprimés et leur importance dans l’évolution des épisodes dépressifs. Valdoxan (agomelatine) est le premier antidépresseur mélatoninergique. Son profil d’action au niveau des récepteurs lui confère une efficacité unique dans la régulation des troubles des rythmes circadiens. Valdoxan, en effet, est le premier antidépresseur agoniste des récepteurs mélatoninergiques MT1 et MT2 et antagoniste des récepteurs sérotoninergiques 5HT2C. Son efficacité antidépressive a été démontrée à court et long termes contre placebo, quelle que soit la sévérité de la maladie, et s’est avérée supérieure à celle de la venlafaxine et la sertraline aux différentes échelles d’évaluation, particulièrement celles utilisées en pratique clinique. Cette efficacité s’associe à des bénéfices cliniques singuliers tels que la régulation non sédative du cycle veille-sommeil et l’amélioration du fonctionnement diurne, dès la première semaine de traitement. Valdoxan n’altère pas les fonctions sexuelles ni la libido, il n’in-duit pas de syndrome de manque à l’arrêt du traitement ou de prise de poids, et il est bien toléré, ce qui en fait un traitement réellement innovant de la dépression, permettant un soulage-ment précoce des symptômes ainsi qu’une rémission complète et prolongée.
The length of such phases remains controversial. However, recommendations for the length of therapy vary widely from 4 to 12 months, according to different authors. Some consider 4 to 9 months of continuation antidepressant treatment to be sufficient. Others recommend approximately 6 months of continuation therapy if there are residual symptoms, and 4 months if there is complete remission with no residual symptoms. More recently, prudent authors have recommended 9 to 12 months of continuation therapy whether residual symptoms are present or not. During this phase, the antidepressant should be continued at the same dose that induced remission. All studies have shown considerable benefit from continuation therapy, with relapse rates at least halved. Continuation psychotherapy can be added to continuation medication following an acute phase response, whether to a single medication or a combination.

In certain situations, there is no need for continuation antidepressant treatment to be followed by maintenance therapy: (i) patients presenting with a first nonsevere depressive episode and aged <55 years old (for some authors <50 years old and for others <60 years old). Some authors recommend continuation treatment for 4 to 6 months in this group of patients; and (ii) patients presenting with a second nonsevere depressive episode after >3 years of remission (for some authors, more than 5 years). Some authors recommend continuation treatment for 6 to 12 months in this group of patients. There is a 30% to 80% chance that these two groups of patients will not show relapse or recurrence during 5 years of follow-up after their last depressive exacerbation. After a full continuation phase, antidepressant treatment discontinuation should then be gradual, and if there is a return of the depressive symptoms, augmentation and enhancing adherence to treatment, adding psychotherapy like interpersonal or cognitive therapy (with better evidence for the latter), and augmenting current antidepressant treatment with adjunctive pharmacotherapy. Other important risk factors for relapse may include comorbid personality, somatic or social disorders, and recurrent depression. Lifestyle recommendations for maintaining remission may include regular physical exercise, more balanced dietary habits, more healthy sleep, as well as better planning and organization of different daily life activities.

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one should revert to the effective dose with a further attempt at withdrawal after at least a further 4 to 6 months of continuation treatment (a further 9-12 months according to some authors). Clinical experience indicates that this phenomenon usually reflects impending relapse. If such patients relapse again during a later drug withdrawal trial, a period of maintenance treatment then becomes appropriate.

Maintenance, prophylactic, or preventive therapy is either of lifetime duration or for at least 5 years. Lifetime maintenance treatment is indicated in the following situations: (i) patients presenting with three or more depressive episodes; (ii) patients presenting with their first depressive episode over the age of 55 years (for some authors this is >60 years of age); and (iii) patients presenting with a second depressive episode when over the age of 40 years.

In the following situations, treatment should be maintained for at least 5 years (3 years for some authors and 4 years for others): (i) patients presenting with a second depressive episode while aged less than 40 years; (ii) patients presenting with a second depressive episode after less than 3 years (for some authors <5 years) of maintained remission; (iii) patients presenting with a second depressive episode after more than 3 years of remission (for some authors >5 years) but experiencing a severe episode (presence of marked suicidal thoughts/actions, psychotic, melancholic or catatonic features, etc); and (iv) patients presenting with a severe first depressive episode. A total of 70% to 90% of these 4 groups of patients are at risk of relapse or recurrence within in 5 years if medication is stopped.

In all cases of maintenance therapy, the antidepressant should be maintained at the same dosage that induced remission.1

What results should a clinician expect in terms of remission?

Complete or full remission1 means that the patient no longer meets the criteria for a depressive disorder and has minimal symptoms at most during 2 months or more. We generally consider that full remission has occurred either when the Hamilton Rating Scale for Depression (HAM-D) score is less than 8, the 9-item Patient Health Questionnaire (PHQ-9) score is less than 5, or the Beck Depression Inventory (BDI) score is less than 9.

The three items most frequently judged by patients to be very important in determining remission are the presence of features of positive mental health such as optimism and self-confidence, a return to one's usual, normal self, and a return to usual levels of functioning.

A patient is considered to be in recovery when remission is maintained for beyond 6 months. The term partial remission means either that the patient no longer meets the criteria for a depressive disorder and has minimal symptoms at most for less than 2 months, or has more than just minimal symptoms for 2 months or more. We generally consider that partial remission has occurred when the HAM-D score is over 7 (between 8 and 17 or 18).

Response means that there is a robust improvement in depressive symptoms with treatment (a reduction of 50% or more in HAM-D or Montgomery–Åsberg Depression Rating Scale [MADRS] scores). Partial response means an improvement in depressive symptoms with treatment, but without reaching response (only 25%-49% reduction in symptoms). Nonresponse means a relative lack of symptom improvement (less than 25% reduction in symptoms). As we can see, residual symptoms may persist even after the patient has achieved full remission, as defined by even the most conservative criteria. Their prevalence in remitted patients is estimated to be 30% to 50%.

Relapse occurs when depressive symptoms fulfilling the DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria for a major depressive disorder arise during either partial or full remission. Recurrence occurs when depressive symptoms fulfilling the DSM criteria for a major depressive disorder arise during the period of recovery. Rebound means a return of the original depressive symptoms but with greater intensity, and withdrawal refers to the development of different symptoms that are related to the stopping of a drug treatment.

When is adjunctive therapy such as psychotherapy needed?

The two main recommended adjunctive psychotherapies in depression are interpersonal therapy and cognitive therapy. Their indication in managing residual symptoms and preventing relapse and recurrence is, however, less well established. Trials of interpersonal therapy for the prevention of recurrence have shown some benefits, but the effects are weaker than those of drugs, and any additional benefit in combination with drugs is limited.

There is better evidence for the effects of cognitive therapy in preventing relapse and recurrence, and there is an emerging indication for its addition to antidepressants, particularly when residual symptoms are present. One randomized, controlled study of cognitive therapy involved 158 patients with recent major depression who were partially remitted with antidepressant treatment but who had residual symptoms of 2 to 18 months’ duration. Patients randomized to continue antidepressant therapy with the addition of cognitive therapy (16 sessions during 20 weeks with 2 subsequent booster sessions) showed significantly reduced relapse rates at 68 weeks compared with those who continued pharmacotherapy alone (29% vs 47%).

Although the cognitive therapy group showed a more significant increase in remission rates at 20 weeks, the increase was comparatively small and not reflected in the mean symptom ratings, particularly on ratings of worthlessness and hopelessness. It seems that the preventive effects of cognitive therapy on relapse are more powerful than the immediate effects on residual symptoms. In a longitudinal study, a total of 40 subjects with residual symptoms were randomized either to modified cognitive therapy targeting anxiety and irritability, or to clinical management. Modified cognitive therapy significantly reduced residual symptoms, as well as relapse and recurrence rates at 4 and 6 years, compared with the clinical management group (35% vs 70%).

In a subsequent study of recurrent depression, a total of 40 patients were randomized either to a therapeutic strategy that included cognitive therapy, lifestyle modification, and well-being therapy, or to a control group. Modified cognitive therapy significantly reduced recurrence from 80% to 20% during 2 years.

What kinds of lifestyle recommendations are helpful for maintaining remission in patients?

The first recommendation is regular physical exercise. When prescribing exercise, several caveats apply:
• Anticipate barriers, as hopelessness and fatigue can make physical exercise difficult.
• Keep expectations realistic, as some patients are vulnerable to guilt and self-blame if they fail to carry out the regimen.
• Introduce a feasible plan: walking alone or in a group, is often a good option. Paying attention while walking to colors, smells, shapes, sounds, and people may be ideal.
It seems that the risk and severity of residual symptoms is significantly less with serotonin and norepinephrine reuptake inhibitors than with selective serotonin reuptake inhibitors; the ideal scenario would be an antidepressant that addressed residual symptoms at the same time as other symptoms, thus removing the need for adjunctive therapy.

When should the clinician and the patient suspect a relapse?

Patients at risk of relapse are those who present with:
(i) three or more depressive episodes; (ii) a second depressive episode occurring after the age of 40 years or one that is associated with severe symptoms, or one that occurs less than 3 years after remission from their first episode (for some authors, less than 5 years); (iii) a first depressive episode occurring after the age of 50 to 60 years (or before 20 years of age according to certain authors); (iv) a longer depressive episode; (v) residual symptoms at remission; their presence appears to affect early short-term relapse rather than overall long-term risk of recurrence or number of recurrences, and to be responsible for impaired long-term social functioning. There is some conflict in the literature concerning factors like initial severity of depression, life stressors, and personality as predictors of residual symptoms. In addition, residual symptoms are prevalent both in patients who have received psychotherapy, as well as those treated with pharmacotherapy; (vi) relapse at medication withdrawal; (vii) family history of bipolar disorder or recurrent depression; (viii) associated disorders on axis 1 or 2; and (ix) bad social adjustment, persistent stressful life events, or absence of social support.

What therapeutic approach should be used for residual symptoms?

We should first try to address treatment-emergent side effects. Indeed, significant overlap exists between the residual symptoms of a depressive episode and the side effects of antidepressants. A systematic assessment of symptoms prior to beginning pharmacological treatment can help to distinguish between residual symptoms and treatment side effects. If dose optimization improves a patient’s symptoms, one may assume that they are likely to have been residual. On the other hand, if op-timization has no effect or worsens symptoms, clinicians may assume that these symptoms probably represent side effects of pharmacological therapy, as the intensity of the side effects is typically dose-dependent. Second, we should diagnose and treat any comorbid medical or psychiatric conditions, such as substance abuse, since these conditions may cloud the assessment of symptoms, whether related to the underlying depressive disorder or antidepressant treatment.

If it is decided that symptoms are likely to be residual, clinicians may want to optimize the antidepressant dose and duration, assess and enhance adherence to treatment, add psychotherapy (cognitive or interpersonal therapy), and augment current therapy with adjunctive pharmacological treatment. By contrast, if symptoms are likely to be side effects of pharmacological treatment, clinicians may want to decrease the antidepressant doses or switch the patient to another antidepressant. Adjunctive treatment, however, may improve such symptoms regardless of the underlying etiology. Such adjunctive treatment includes the following:
(i) for anxiety, either a benzodiazepine (like lorazepam, alprazolam, or clonazepam), buspirone, gabapentin, or an antipsychotic (olanzapine, quetiapine); (ii) for insomnia, we can add either an hypnotic (like zolpidem or zopiclone), or lorazepam, or sedative antidepressants (like mirtazapine, mianserin, or trazodone); (iii) for fatigue and somnolence, we can add either methylphenidate, modafinil, bupropion, or reboxetine; (iv) for apathy, we can also add either methylphenidate, modafinil, bupropion, or reboxetine; and (v) for cognitive disturbances, we can add either anticholinesterase medications (like donepezil), methylphenidate, modafinil, bupropion, reboxetine, or memantine.

**REFERENCES**

orsqu’un patient a répondu à un traitement antidépresseur d’attaque, une phase de consolidation est systématiquement indiquée et doit, dans certaines situations cliniques, être poursuivie par une phase d’entretien. Si la durée de ces différentes phases ne fait pas l’objet d’un consensus, la posologie du traitement antidépresseur, quant à elle, doit être la même pendant les phases de consolidation et d’entretien que celle qui a permis la rémission. Une rémission complète signifie que le patient ne remplit plus les critères d’un trouble dépressif et ne présente que des symptômes minimaux, pendant 2 mois ou plus ; elle correspond généralement à un score inférieur à 8 à l’échelle HDRS (Hamilton Rating Scale for Depression). Les symptômes résiduels, qui peuvent donc persister même après la rémission complète, sont considérés comme un facteur de risque important de rechutes et de handicap social à long terme. La prévalence des symptômes résiduels chez les patients en rémission est estimée entre 30 et 50 %. On y trouve principalement l’insomnie, l’anxiété, les troubles cognitifs, l’apathie, la fatigue et la somnolence. Leur prise en charge comporte l’optimisation de la dose et de la durée du traitement antidépresseur, l’évaluation et l’amélioration de l’observance du traitement, l’ajout de psychothérapies interpersonnelles ou cognitives (l’efficacité de ces dernières étant mieux prouvée) et l’association au traitement antidépresseur en cours d’un traitement pharmacologique adjuvant. La personnalité comorbidite, les troubles somatiques et sociaux et la dépression récurrente sont également des facteurs de risque important de rechute. Pour contribuer au maintien de la rémission, on peut recommander un exercice physique régulier, de meilleures habitudes alimentaires, un sommeil plus équilibré ainsi qu’une meilleure planification et organisation des activités de la vie quotidienne.

PRISE EN CHARGE CLINIQUE DES PATIENTS APRÈS LA RÉMISSION D’UNE DÉPRESSION
Several investigations have suggested the usefulness of a sequential way of integrating pharmacotherapy and psychotherapy in depression. Administration of treatments in sequential order is a common practice in clinical medicine, particularly when treatment fails. This sequential administration of treatments also occurs in clinical psychiatry. It may involve switches to different types of drugs, as is often the case in drug-refractory depression. An increase or decrease in dose, augmentation, or change to a different drug. There are also examples of changes of types of treatment: use of antidepressants after unsuccessful cognitive behavioral therapy (CBT) in depression, and of CBT in the management of drug-resistant major depressive illness.

The recent findings of the largest depression trial, Sequenced Treatment Alternatives to Relieve Depression (STAR*D), have provided a dramatic illustration of the difficulties in achieving recovery from depressive illness by using pharmacological strategies. The aim of the trial was to apply the best pharmacological strategies to obtain remission in major depression. A sample of 3671 patients was treated with citalopram in an open fashion: only 36.8% of patients remitted. Those who did not recover were submitted to four sequential steps involving switching, augmentation, and combination strategies, based on available literature. The recovery rate was low and difficult to attribute to specific effects of citalopram, since there was a variety of nonspecific therapeutic ingredients, as in other major trials.

Because of the type of randomization that was chosen (equipoise-stratified randomization strategy), the role of cognitive therapy could not be established, since the patients who opted for it were too few (less than one third of participants). The STAR*D results were rather disappointing. The cumulative rate of remission after 4 sequential steps was 67%. However, when sustained recovery was considered (taking into account relapse rates while on treatment), the cumulative rate was 43%. This means that the strenuous efforts after step one (open treatment with citalopram) yielded an additional 6% of sustained recovery.

In clinical medicine, there is also, however, another type of sequential treatment, which is not related to the partial remission or failure associated with a specific therapy (sequence is performed regardless of the outcome of the first component, as a preplanned strategy). This type of approach is based on the awareness that one course of treatment is unlikely to yield full disappearance of symptomatology. A related assessment strategy is the staging method, whereby a disorder is characterized according to seriousness, extension, and features.

There is increasing literature on the bleak long-term outcome of depression in terms of relapse and recurrence. This unsatisfactory outcome seems to be associated with the presence of substantial residual symptomatology. If residual symptoms are the rule after completion of drug or psychotherapeutic treatment, and their presence has been correlated with poor outcome—as residual symptoms upon recovery may progress to become prodromal symptoms of relapse—then treatment directed toward residual symptoms may yield long-term benefits. Treatments that are aimed at potentially different symptoms, such as pharmacotherapy and psychotherapy, may thus be used in a sequential order. One type of treatment (eg, psychotherapy) may be employed to improve symptoms that the other type of treatment (eg, pharmacotherapy) was unable to affect. Several studies substantiate the clinical advantages of the sequential use of psychotherapy after pharmacological treatment. There has been little research on other forms of sequential treatment in depression. It has also been suggested that the most effective drugs in treating acute depression may not be the most suitable for postacute or continuation treatment. The sequential treatment of depressive illness does not fall within the realm of maintenance strategies. It is an intensive two-stage approach, which is based on the fact that one course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to hold a solution to the complex array of symptoms in patients with depression. The sequential model entails considerable implications for assessment and treatment planning.

**Keywords:** depression; recovery; staging; sequential model; cognitive behavioral therapy; wellbeing therapy

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Instead of administering different therapies together, their sequential administration is planned, based on some specific effects induced by each of them that provide additional benefits in the course of time. Staging has the potential to improve the logic and timing of interventions. The phenomenological development of unipolar depression may be categorized according to stages (Table I). A drug that may be effective in stage 2 major depressive episode (previously untreated) may not be as effective in a patient with stage 4 recurrent major depression who has been submitted to previous trials. Most of the patients in STAR*D were in stages 4 or 5 of Table I. Pharmacological manipulations, either by switching or augmentation (steps 1 and 2), may propel depressive illness into a refractory phase, characterized by low remission, high relapse, and high intolerance (steps 3 and 4).

**Rationale for sequential treatment**

Standard treatment of depression, even in specialized settings, seems to yield modest and temporary benefits and to leave a large amount of residual symptomatology, which appears to be one of the strongest predictors of an unfavorable outcome. These findings have led to the hypothesis that residual symptoms upon recovery may progress to become prodromal symptoms of relapse, and that treatment directed toward residual symptoms may yield long-term benefits. Treatment that is potentially aimed at producing different effects (eg, pharmacotherapy and psychotherapy) may thus be used in a sequential order. One type of treatment (eg, psychotherapy) may be employed to improve symptoms that the other type of treatment (eg, pharmacotherapy) was unable to affect. This may be particularly important when treatments provide different modulations of cortical-limbic pathways, such as CBT and antidepressant drugs in major depression.

Even though psychotherapy-pharmacotherapy combinations have been shown to be more effective than monotherapy in a number of psychiatric disorders, the effect size observed favoring combined treatment has been generally rather modest in mood and anxiety disorders. Another line of evidence potentially supporting the sequential model in affective disorders is the increasing awareness of the role of comorbidity.

In a controlled therapeutic trial, 40 patients with major depressive disorder who had been successfully treated with antidepressant drugs were randomly assigned to either CBT or clinical management of residual symptoms. In both groups, antidepressant drugs were tapered and discontinued. The group that received CBT treatment had a significantly lower level of residual symptoms after drug discontinuation in comparison with the clinical management group. CBT also resulted in a lower rate of relapse, with achievement of statistical significance at a 4-year follow-up. These differences faded at a 6-year follow-up. However, when multiple relapses were considered, patients in the CBT group had a significantly lower number of depressive episodes than those in the standard clinical management group.

The aim of this approach was to spend CBT resources when they are most likely to make a unique and separate contribution to patient wellbeing and to achieve a more pervasive recovery. This sequential approach was also applied to 40 patients with recurrent major depression (according to the criteria outlined by Frank et al) by the same group of investigators. Patients were randomly assigned to either CBT for residual symptoms—supplemented by lifestyle modification and wellbeing therapy—or clinical management. In both groups, antidepressant drugs were tapered and discontinued. At a 2-year follow-up, CBT resulted in a significantly lower relapse rate (25%) than did clinical management (80%). The differential relapse rate was found to be significantly related to the abatement of residual symptoms. At a 6-year follow-up, CBT still resulted in a significantly lower relapse rate (40%) compared with clinical management (90%).

Other groups of investigators lent support to the sequential use of pharmacotherapy and psychotherapy for relapse prevention in unipolar depression. Paykel et al randomized 158 patients with recent major depression, partially remitted with antidepressant treatment but with residual symptoms, to clinical management or clinical management associated with cognitive therapy. Patients received continuation and maintenance antidepressants during a 1-year follow-up period. The relapse rate was 47% in the clin-

### Selected Abbreviations and Acronyms

- **ACT**: acceptance and commitment therapy
- **CBT**: cognitive behavioral therapy
- **DSM-IV**: *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*
- **ETAU**: enhanced treatment as usual
- **IPT**: interpersonal psychotherapy
- **MBCT**: mindfulness-based cognitive therapy
- **STAR*D**: Sequenced Treatment Alternatives to Relieve Depression (study)
- **TAU**: treatment as usual

**Table I. Stages of primary unipolar depression.**

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prodromal phase (anxiety, irritable mood, anhedonia, sleep disorders)</td>
</tr>
<tr>
<td></td>
<td>a. No depressive symptoms</td>
</tr>
<tr>
<td></td>
<td>b. Minor depression</td>
</tr>
<tr>
<td>2</td>
<td>Major depressive episode</td>
</tr>
<tr>
<td>3</td>
<td>Residual phase</td>
</tr>
<tr>
<td></td>
<td>a. No depressive symptoms</td>
</tr>
<tr>
<td></td>
<td>b. Dysthymia</td>
</tr>
<tr>
<td>4</td>
<td>a. Recurrent depression</td>
</tr>
<tr>
<td></td>
<td>b. Double depression</td>
</tr>
<tr>
<td>5</td>
<td>Chronic major depressive episode (lasting at least 2 years without interruptions)</td>
</tr>
</tbody>
</table>

**Use of psychotherapy after pharmacological treatment**
ical management group and 29% with CBT. There was a small but statistically significant effect on residual symptom levels. Cost effectiveness analyses showed substantial benefits with the CBT approach. At a 6-year follow-up, the effects on prevention of relapse and recurrence were found to persist up to 3 and a half years after the end of CBT.

Similar results were obtained with mindfulness-based cognitive therapy (MBCT). Teasdale et al randomized 145 patients in remission or recovery from major depression to treatment as usual (TAU) or TAU supplemented by MBCT. For patients with 3 or more previous episodes of depression, who constituted 77% of the sample, relapse rates were 66% for the TAU controls and 37% for the patients also receiving MBCT. However, there were no significant differences in outcome for patients with only two previous episodes of depression. Since MBCT was administered in groups, this study provided the first demonstration that the sequential model may yield beneficial results also in the group format. The favorable results concerning MBCT were replicated in a subsequent study.

In another randomized controlled trial, 187 patients were randomized to TAU including continuation of pharmacotherapy, or to TAU associated with group cognitive therapy. During a 2-year follow-up period, cognitive therapy resulted in a significant protective effect, which increased with the previous number of depressive episodes experienced. Bockting et al identified a significant protective effect of cognitive therapy in patients with at least two previous episodes who remitted on various types of treatments (n=172). Preventive cognitive therapy protected against the influence of a consistently found risk factor for relapse/recurrence (the number of depressive episodes). This result underlines the potential of psychological preventive interventions.

One study, however, has failed to substantiate the clinical advantages of the sequential model in unipolar depression. A total of 132 patients with major depression who achieved remission with fluoxetine were randomized to receive CBT and medication or medication management alone, and were followed for up to 28 weeks. Relapse rates did not differ between the two groups, even though the addition of CBT was associated with attributional style gains. A major limitation of this study, however, was the duration of follow-up (in previous studies, maximal gains tended to occur at a later point).

The results of the randomized controlled trials therefore lend support to the use of a sequential treatment model (pharmacotherapy followed by psychotherapy) for preventing relapse in unipolar depression. This approach appears to be particularly important in recurrent depression. However, since incomplete recovery from the first lifetime major depressive episode was found to predict a chronic course of illness during a 12-year prospective naturalistic follow-up study, this sequential approach may be indicated whenever substantial residual symptomatology is present.

The advantages of keeping patients on their medication during psychotherapy, versus tapering and discontinuation, have not been directly compared in sequential studies. Some inferential indications may come from a study by Blackburn and Moore. A total of 75 outpatients with recurrent major depression were allocated to 3 groups: short-term and maintenance (2 years) treatment with antidepressant drugs, CBT in the short-term and maintenance phases, and antidepressant use in the short-term phase with CBT for maintenance. CBT displayed a similar prophylactic effect to maintenance medication. There were no significant differences among treatments. These results have been confirmed in a trial by Hollon et al involving 104 patients who responded to treatment (either CBT or medication). Patients who responded to CBT were withdrawn from treatment and compared with medication responders who had been randomly assigned to either continuation medication or placebo withdrawal during a 12-month period. Patients who survived the continuation phase without relapse were withdrawn from all treatment and monitored during a 12-month naturalistic follow-up period. Patients who completed CBT were significantly less likely to relapse (31%) than patients on placebo (76%) and no more likely to relapse than those who carried on taking continuation medication (47%). Survival analysis of the naturalistic follow-up indicated that CBT, unlike antidepressant drugs, had an enduring effect extending beyond the end of treatment. The results of these two studies therefore suggest that discontinuation of antidepressant drugs may be feasible in subgroups of patients when CBT is provided.

A novel indication for the sequential model was provided by a very small pilot study, which concerned 10 patients with recurrent depression who relapsed while taking maintenance antidepressant drugs. They were randomly assigned to a dose increase and clinical management, or to CBT and maintenance of the antidepressant drug at the same dose. Four of five patients responded to a larger dose, but all had relapsed again at that dose by a 1-year follow-up. Four of five patients responded to CBT, but only one relapsed during follow-up. In another recent investigation, the feasibility of a family intervention approach to the loss of clinical effect during long-term antidepressant therapy was explored. A total of 20 outpatients with recurrent major depressive disorder who lived with a partner and had relapsed while taking antidepressant drugs were randomly assigned to (i) family intervention approach according to the McMaster Model and maintenance of the antidepressant drug at the same dosage or (ii) dose increase and clinical management. Seven out of 10 patients responded to an increased dosage; all but 1 relapsed again on that dosage during follow-up. Seven out of 10 patients responded to family intervention, but only 1 relapsed during follow-up. The data from these pilot studies have to be confirmed with large-scale controlled studies, but may suggest that the application of a sequential model is feasible when there is a loss of clinical effect during long-term antidepressant treatment. Treatment for patients with psychotic depression is urgently needed due to the
increased risk of morbidity and mortality associated with this population. Patients with psychotic depression show a poorer response to antidepressant treatment with tricyclics or selective serotonin reuptake inhibitors alone compared with nonpsychotic depressed individuals.

Pilot data by Gaudiano et al recently suggested that patients with psychotic depression can benefit from modified CBT approaches (acceptance and commitment therapy, ACT). In this pilot trial, 40 patients were randomly assigned to enhanced treatment as usual (ETAU) or ETAU plus individual ACT sessions. ACT was associated with clinically significant reductions in acute symptom severity and impairment compared with treatment as usual. Gaudiano et al found it appropriate to begin therapy with most hospitalized patients once they were able to participate in other group therapy on the unit, after initial psychiatric stabilization with medications. After acute psychotic symptoms dissipate and antipsychotic medication is withdrawn, psychotherapy can be started to help patients monitor residual symptoms and learn to cope more effectively with stressors to prevent symptom recurrence.

**Use of pharmacotherapy after psychological treatment**

There is little research on the sequential use of psychotherapy and pharmacotherapy, despite the fact that successful psychotherapy is also associated with substantial residual symptomatology. Frank et al used a successive cohort approach to compare two similar groups of female patients with recurrent unipolar depression: one in which the combination of interpersonal psychotherapy (IPT) and pharmacotherapy was initiated at the beginning (n=180), and a second in which IPT alone was first provided, with only those not remitting being given the combination treatment (n=159). The remission rate was significantly higher in the latter group. The results thus suggest that the strategy of offering IPT to women with recurrent depression, adding pharmacotherapy only in the case of incomplete remission, might be advantageous.

**Sequential use of two pharmacological strategies**

The sequential use of pharmacological strategies in affective disorders has been traditionally limited to instances of treatment resistance. A notable exception has been the use of lithium to reduce relapse in unipolar depression. It has also been suggested that the most effective drugs in treating acute depression may not be the most suitable for post-acute or continuation treatment. During a 6-year follow-up in a randomized trial comparing the sequential use of pharmacotherapy and cognitive behavioral treatment versus clinical management in patients with recurrent depression, no antidepressant drugs were used unless a relapse ensued. Patients were then treated with the same antidepressant drug that had been used in the previous episode. Clonazepam was added to the treatment regimen and continued when the antidepressant drug was stopped. The mean survival time after introduction of clonazepam was significantly longer than that before the first relapse.

**Sequential use of two psychotherapeutic techniques**

Current psychotherapeutic strategies, particularly in the CBT realm, use several elements from the beginning (e.g., cognitive restructuring, exposure, relaxation, etc.). It would be of interest to verify whether the sequential use of single treatment components can yield significant advantages, both in mood and anxiety disorders. For instance, in a modified CBT approach to drug-resistant major depression, therapeutic ingredients were introduced at different times (behavioral activation first and cognitive restructuring later).

**Implications for assessment and treatment planning**

The literature that has been reviewed here has potential implications for clinical practice, but it should be interpreted with caution in view of several issues. First of all, there are insufficient studies exploring the various types of sequential approach in unipolar depression, with the exception of pharmacotherapy followed by psychotherapy. Further, the sequential design is exposed to the risk that one treatment is provided in a more expert manner than another (e.g., the use of psychotropic drugs compared with psychotherapy). Third, certain types of treatment that have been used, such as mindfulness therapy and wellbeing therapy, may not be widely available, and there are difficulties entailed in their translation from the “expert” site to clinical practice. Fourth, when the results of a sequential treatment are compared with those of a minimal intervention control group (such as clinical management or TAU), there is the possibility that the treatment effect may have been achievable with any active treatment and may not be specific to the treatment at hand. Finally, several of the aforementioned studies were based around patients who had responded to initial treatment, and this might have led to an undervaluation of the fact that patients at high risk may have dropped out early.

Nonetheless, there are considerable implications for assessment and treatment planning that are worthy of clinical attention. The sequential model calls in fact for a substantial modification of the flat, cross-sectional approach based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition) criteria only, which ignores the longitudinal development of depressive illness, previous episodes, and responses to previous treatments. A satisfactory assessment requires multiple points of observation during the course of affective illnesses. Such observations may disclose psychopathological features that are overshadowed by the acute manifestations of the affective disorder. As a result, three assessment phases are required, with modalities that depart from those commonly
used in psychiatric practice. The key issue is in fact to match treatment ingredients with psychopathological findings.

**Initial assessment**

The majority of patients with mood and anxiety disorders do not qualify for one, but for several axis I and axis II disorders. However, there is comorbidity that wanes upon successful treatment of depression and comorbidity that persists, in syndromic or subsyndromic forms (residual symptoms). Clinical differentiation of such morbidity requires a shift from the current psychometric model (where severity is determined by the number of symptoms and not by intensity or quality) to a clinimetric model, which may allow a definition of the progression, extent, and severity of depressive illness.

As a response to the current flat diagnostic evaluation, Emmelkamp et al. have introduced the concept of macro-analysis (a relationship between co-occurring syndromes is established on the basis of where treatment should commence first). The planning of sequential treatment thus requires determination of the symptomatic target of the first-line approach (eg, pharmacotherapy), and tentative identification of other areas of concern to be addressed by subsequent treatment (eg, psychotherapy). Organization of different DSM syndromes by macro-analysis is thus the key to successful implementation of the sequential model.

**Re-assessment after the first line of treatment has been completed**

It is of the utmost importance that the patient be reassessed after the first line of treatment has been completed, in order to establish the level of remission in the patient and whether residual symptoms are occurring and further treatment is necessary. In two studies concerned with the sequential treatment of depression, reassessment was performed after 3 months of drug treatment, when maximal benefits were likely to be present. There are several major obstacles to a satisfactory assessment of the patient at this stage. The first lies in the exploration of only a few target symptoms, instead of the full spectrum of psychopathology (as if he or she were a new patient). The second pitfall derives from the fact that the hidden conceptual model in clinical assessment is psychometric, in which severity is determined by the number of symptoms, not by their intensity or quality. Further, the assessment of subclinical symptomatology, as frequently occurs in the setting of remitted or partially remitted disorders, cannot exclude consideration of the symptoms’ longitudinal development (prodromal phase, the fully developed disorder, and residual states). Detre and Jarecki provided a model for relating prodromal and residual symptomatology in psychiatric illness, defined as the rollback phenomenon: as the illness remits, it progressively recapitulates (though in a reverse order) many of the stages and symptoms that were seen during the time it developed. Finally, in clinical practice as well as in research, collection of symptom information is performed during a clinical interview. However, self-observation, in which the patient is instructed to report in a diary the most important episodes of distress that may have ensued in a specific time period, such as a couple of weeks, is an important source of information concerned with allostatic load.

**Final assessment after the second line of treatment has been completed**

Final assessment should take place after the second line of treatment has been completed; for instance, in a depressed patient when psychotherapy following pharmacotherapy has been performed and medications have been discontinued. If substantial residual symptomatology persists despite clinical response, then new treatment strategies, such as long-term, indefinite drug therapy, should be discussed with the patient.

**Conclusion**

The sequential treatment of mood and anxiety disorders does not fall within the realm of maintenance strategies, which have the aim of prolonging clinical responses obtained with treatments. It is an intensive, two-stage approach, which derives from the awareness that one course of treatment with a specific tool (whether pharmacotherapy or psychotherapy) is unlikely to entail a solution to the affective disturbances of patients. The aim of the sequential approach is to add therapeutic ingredients as long as they are needed. Therapeutic targets are not pre-determined, but depend on the response of patients to the first course of treatment.
L e sombre avenir à long terme de la dépression en termes de rechute est de plus en plus démontré. Cette évolution insatisfaisante semble liée à l’existence d’une symptomatologie résiduelle importante. Si les symptômes résiduels sont la règle à la conclusion d’un traitement pharmacologique ou psychothérapeutique et que leur présence est corrélée à un mauvais pronostic (du fait qu’ils puissent évoluer après la guérison), ils peuvent être utilisés dans un ordre séquentiel, l’un (par exemple la psychothérapie) employé pour améliorer les symptômes que l’autre (par exemple la pharmacothérapie) ne peut soigner. Plusieurs études étaient les avantages cliniques de l’utilisation séquentielle de la psychothérapie après la pharmacothérapie. Peu de recherches ont été faites sur d’autres formes de traitement séquentiel de la dépression. Les médicaments les plus efficaces dans le traitement d’attaque de la dépression ne sont pas nécessairement les plus appropriés pour le traitement de la phase de consolidation ou d’entretien. Le traitement séquentiel de la maladie dépressive n’appartient pas aux stratégies de maintenance. Il s’agit d’une approche intensive en deux étapes basée sur le fait qu’un type de traitement spécifique (pharmacothérapie ou psychothérapie) ne peut dénier la solution de l’ensemble complexe des symptômes présentés par les patients dépressifs. Le modèle séquentiel des troubles dépressifs est une évaluation et Planification du traitement.
Ruijin Hospital
From 19th-century French Jesuit Hospital to present-day state-of-the-art Chinese University Hospital

by GU Qian, NI Lidong, and HU Weiguo, China

Ruijin Hospital (瑞金医院), which originated as the medical wing of Aurora University (震旦大学, literally “Thunder of Sunrise”), a French-Catholic institution founded in Shanghai in 1903 and dissolved in 1952, is today affiliated to the Shanghai Jiao Tong University School of Medicine (上海交通大学医学院). Despite changes of name—it began life as l’Hôpital Sainte-Marie, then became Guangci Hospital (廣慈医院, literally, “Great Mercy Hospital”)—it retains vigorous reminders of its French past during the first half of the 20th century when most of its doctors, whether French or Chinese nationals, were not only fluent French speakers but the respected and expert practitioners of a French-accented medicine. The history of Aurora University, its medical school, and hospital provides a fascinating glimpse of enlightened European and Catholic outreach in a largely impoverished oriental metropolis during the early 1900s. It is also a striking example,
within the medical sphere, of accommodation and cross-fertilization between two ancient and contrasting cultures, those of France and China. The founder of Aurora University was a Chinese Jesuit, Joseph Ma Xiangbo (马相伯) (1860-1939). Born into a well-to-do Catholic family, his early education was in the Chinese classics. At the age of 12, he was enrolled in St Ignatius College, newly opened by the French Jesuits in Shanghai. After ordination at the age of 30, he returned to St Ignatius as its principal. Excelling in astronomy, mathematics, and Latin, he set out to translate European scientific works into Chinese. In 1876, however, he left the priesthood, married, and spent the next 21 years working in business and government on behalf of the Chinese Self-Strengthening Movement that advocated learning from the West. In that capacity he traveled abroad, not only to Korea but also to the United States and Europe. But as the Movement waned and after his wife died, Ma Xiangbo rejoined the Jesuits in Shanghai in 1898 and five years later opened the Aurora Academy (Zhendan Xueyuan震旦学院) with the purpose of furthering his original aim of translating the Western books that China needed in its drive toward modernization, and he chose its name, “Thunder of Sunrise,” to mark the Chinese new dawn that he hoped it would usher in.

In 1908, Aurora University introduced a French-style undergraduate curriculum including a three-year preparatory program and a three-year advanced program. The preparatory program included subjects such as French, English, history, philosophy, geography, elementary mathematics, physics, and other natural sciences. On successful completion of this program, students opted between the four majors of the advanced program: humanities, law, medical science, and philosophy. From grade 2 of the preparatory program upwards, all courses except Chinese were taught in French.

Meanwhile the Jesuit Apostolic Vicar of nearby Nanking, Próspero París (姚宗李) (1846-1931), had bought 165 acres of Shanghai land east of the main thoroughfare Jinshenpu Lu金神廟路 (modern Ruijin No. 2 Avenue瑞金二路) in order to found a hospital. The first construction phase consisted of four Western-style two-floor brick-and-timber houses, two of which contained wards for a total of 100 patients. The opening ceremony took place on October 13, 1907. Known initially to Europeans as the “Hospital Sainte-Marie,” it was renamed Guangci Hospital广慈医院 several years later.

Aurora Academy selected a site near the hospital to found a medical school. Its students could do their ward work in the hospital, and the most outstanding graduates were selected as interns. In those early days, two French doctors managed the inpatients while nuns cared for the outpatients, from examination through diagnosis to treatment and dispensing. Wards were arranged hierarchically (missionary ward, first-class male and female wards, second-class civilian wards) and by specialty (obstetrics, isolation, etc). There were also special wards, such as for French armed forces personnel, police officers from Annam (the French protectorate in central Vietnam), and criminals.

The first operating rooms opened in 1918 and catered for three or four major cases daily, primarily in gastrointestinal surgery (hemorrhoids, appendix, bowel, stomach, and biliary tract), but also urinary tract and gynecological surgery. In 1921, Guangci Hospital became one of the first in China to open a department of radiology. Its Pasteur Building housed some celebrated laboratories. The French Concession's
Industry Bureau funded the five-floor St Vincent de Paul building containing 300 beds. The board of directors, set up in the 1930s, included the French consul general, the heads of the Industry Bureau, and relevant Church dignitaries. In 1936, the Hospital founded a nursing school for specialist nurses and medical technicians. By 1940, when Guangci Hospital registered with the Shanghai government, it had become a 780-bed institution and the largest hospital in the Far East.

Having started out as wholly French-Catholic in inspiration and practice, deploying exclusively French treatments dispensed by French doctors and nuns, Guangci Hospital evolved over the years to absorb more and more influence from its Chinese environment. It became a Sino-French institution hosting an uninterrupted and indeed increasing interchange of science and talent that attracted—and continues to attract—some of China’s best medical brains onto both its faculty and student body.

In 1933, Dr Kuang Ankun (况安君), who had obtained his medical degree in Paris, returned home as professor of internal medicine at Aurora University and chief of internal medicine at Guangci Hospital. He transformed the theory and practice of his specialty at the University. His immediate concerns were the prevention and treatment of diseases such as relapsing fever, typhoid, and amebic dysentery, and he was among the first in China to diagnose lupus erythematosus and temporal arteritis, attracting considerable public interest at the time. He was followed in 1935 by Dr Xu Baoyi (徐宝彝), a surgeon with degrees from the University of Lyon, who returned home to become professor of surgical science at Aurora University and chief of surgery at Guangci Hospital. His skill in thyroid and gastrointestinal surgery, including surgery of the biliary tract, earned him a regional and international reputation. He was elected to the International Society of Surgery and chaired the Shanghai Medical Association.

An impressive number of French physicians and surgeons subsequently joined the Aurora University faculty and served on the staff of Guangci Hospital. Their specialties covered surgery, pediatrics, infectious disease, and radiology. Working alongside French or Belgian-trained Chinese nationals, such as the surgeon Dr Fu Peibin (傅培彬), the obstetrician and gynecologist Dr Tang Shiheng (唐世恒), the urologist Dr Cheng Yixiong (程一雄), the otorhinolaryngologist Dr Liu Tao (刘海), and the dermatologist Dr Zhu Zhonggang (朱仲刚), they laid the foundation for the Hospital’s future development.

In 1952, all the faculties of Aurora University (震旦大学), including its medical school, were combined with the faculties of Fudan (复旦), which Ma Xiangbo had helped establish, East China Normal University (华东师范大学), and Shanghai Second Medical College (上海第二医学院). Guangci Hospital (广慈医院) became the College’s affiliated teaching hospital. The College was renamed Shanghai Second Medical University (上海第二医科大学) in 1985, and in 2005 was merged with Shanghai Jiao Tong University (上海交通大学) to be renamed Shanghai Jiao Tong University School of Medicine (上海交通大学医学院). Guangci Hospital itself was renamed Dong Fang Hong Yi Yuan (The East is Red Hospital, 东方红医院) in 1966, then Ruijin Hospital (瑞金医院) in 1972.

In the 1980s, Shanghai Second Medical University reconnected with its roots by recruiting students for a 7-year course in French language and medicine, the first of its kind in China. It has since contracted with some 18 French universities and medical schools to host exchange students and teaching faculty in multiple medical disciplines. Up to two thirds of the University’s foreign exchange medical students have studied in France. In 1996, Ruijin Hospital agreed a staff training and academic exchange scheme with the Paris university hospital authorities. One of the aims spelled out in the Sino-French health cooperation agreement announced by French President Jacques Chirac during his visit to China, when he came to Ruijin Hospital, was to support the French medicine program. Students
on the program not only complete a broader introductory course in the humanities and social sciences, they also receive a firmer foundation in the natural sciences, a more solid grounding in basic medical theory and a more systematic introduction to clinical medicine. At the same time, they become proficient in French, to the extent that they can read French medical documents and communicate in the language. Half the students on the program are given the opportunity to work for periods as hospital doctors in France with all costs borne by the host country.

The program faculty combines staff from the Ruijin Hospital School of Clinical Medicine, notably Drs Wang Zhenyi (王振义), Chen Zhu (陈竺), and other members of the Chinese Academy of Sciences, with teachers from France, in particular during the first year, when the curriculum comprises no fewer than 726 hours of lectures and exercises in basic French. Between 1997 and 2007, France sent over some 120
teaching staff from a wide range of university hospitals. The Ruijin School of Clinical Medicine has also edited and published the French version of major textbooks in medicine and surgery. In conjunction with universities in Lyon and Paris, it has set up the SPIRAL resource server to enable its students to access exactly the same teaching programs and course materials, including interactive video and audio lectures, to the extent that its students are virtually sitting alongside their French counterparts.

Today Ruijin Hospital is a 1600-bed general teaching hospital occupying a 30-acre site with a floor area of 60 acres and over 3000 staff, including some nationally and internationally known figures such as Dr Chen Zhu (陈竺), but also Drs Wang Zhenyi (王振义) and Chen Saijuan (陈赛娟), both members of the Chinese Academy of Engineering. In addition to its 34 clinical departments, the Hospital has nine departments of medical technology. It also encompasses six Shanghai institutes (Traumatology and Orthopedics, Hypertension, Endocrine and Metabolic Diseases, Burns, Hematology, and Digestive Tract Surgery), plus two of the Ministry of Health’s Key Laboratories (Human Genome, and Endocrine and Metabolic Diseases). Ruijin Hospital has been renowned for its expertise in treating major burns ever since saving steelworker Qiu Caikang (邱财康) in 1958, a case that instantly assumed iconic status in the country’s medical culture. After pioneering organ transplantation in the 1970s, the Hospital became renowned in the 1990s for breakthroughs in the management and molecular biology of leukemia. In terms of sheer volume, the Hospital has around 60 masters’ and PhD students at any one time, each with an accredited supervisor. Over 2 million patients annually attend its outpatient and emergency departments, and around 25 000 undergo surgery.

Hospital staff have an impressive array of over 300 awards to their credit, including the E. I. Evans Prize (American Burns Association), the G. Whitaker International Burns Prize (Italy), Catherine Cancer Prize (USA), the Charles Rodolphe Brupbacher Foundation Prize (Switzerland), the Prix de l’Oise (French Ligue Nationale Contre le Cancer), the Simone and Cino del Duca Foundation Prize (France), and the He Liang and He Li Fund (何梁何利基金) Technology Prize (Hong Kong).

In November 2002, France inaugurated its first large-scale cooperation structure, the Sino-France Research Center for Life Science and Genome Research, which was set up in Ruijin Hospital. This sealed 10 years’ collaboration between Ruijin, its Institute of Hematology under Dr Chen Zhu, and French National Center for Scientific Research (CNRS) laboratories UPR9051 and UMR7151 at
Saint-Louis Hospital in Paris. An important research focus, headed by Chen Zhu, has been in acute promyelocytic leukemia, with particular regard to the mode of action of arsenic trioxide, the role of cyclic adenosine monophosphate (cAMP), and the ubiquitination reaction. These and other studies have led to publications in *Science, Cancer Cell, Proceedings of the National Academy of Sciences, EMBO Journal, Journal of Experimental Medicine, Journal of Clinical Investigation, Blood, American Journal of Human Genetics, Oncogene,* and *Leukemia.*

In 2004, Ruijin Hospital signed a cooperative agreement with Servier, the largest independent French pharmaceutical company, to sponsor study visits to leading French hospitals by six Ruijin endocrinologists and cardiologists. Servier has been present in China for over 20 years, during which time it has won the trust of the country’s pharmacists and physicians. Over the last two decades, it has been working extensively with Chinese academia via the Sino-French exchange program and cooperative research in epidemiology, public health, and other fields. Servier representatives regularly visit close on 1400 hospitals in China’s northern, southern, and eastern provinces.

France has been unstinting in its recognition of the outstanding contributions made by Ruijin Hospital staff in fostering Sino-French partnerships. It has made Drs Kuang Ankun, Li Hongwei (李宏为), and Chen Zhu *chevaliers* of the Legion of Honor, while Drs Lin Yanzhen (林言箴), Li Hongwei, and Chen Zhu have been elected members of the French Academy of Sciences. In many ways, Chen Zhu personifies the success of Sino-French cooperation. After medical studies in Jiangxi, he took a postgraduate course at Shanghai Second Medical University from where he went to Paris to earn a doctorate in hematology at Saint-Louis Hospital. On 29 June 2007, he was appointed China’s Minister of Health, the second non-Communist Party member—alongside Wan Gang (万钢)—appointed Minister of Science and Technology on 27 April 2007—to rise to such a key position since the late 1970s.

In June 2005, Ruijin Hospital and Shanghai Second Medical University hosted a week-long Sino-French medical meeting cosponsored by the Chinese and French Ministries of Health. The sessions, largely devoted to HIV-AIDS (human immunodeficiency virus—acquired immunodeficiency syndrome), emergent diseases, and the practicalities of medical exchange programs between the sponsor nations, were attended by key figures in these areas, not least Chen Zhu, and, on the French side, Prof Vincent Deubel, director of the Shanghai Pasteur Institute, and key advisers on health to the French government.

In 2007, Ruijin Hospital celebrated its 100th birthday in cultural continuity with the old Hôpital Sainte-Marie. French physicians were on hand to witness the unveiling of the centenary monument inscribed with the hospital’s significant contributions (such as China’s first kidney, liver, and heart transplants), to which their country had in no small measure contributed. It would have been clear to those present that France had ceased to be the unchallenged mentor in the Sino-French medical relationship. Exchange was no longer one-way. Increasing numbers of French physicians and bioscientists are now coming on training visits to Ruijin Hospital, to feed on the knowledge and experience of their Chinese colleagues, and to bring back to France a love and appreciation for what this once-French, but now wholly Chinese hospital is achieving in terms of both medical science and the care of its surrounding population.

**Cover of the Program of the 27th France-China Medical Days (27èmes Journées Médicales France-Chine) in Beijing, Wuhan, and Shanghai, 21-28 September 2008, an illustration of one among many longstanding partnerships between China and Servier.**
Académie Auroré (Zhendan Xueyuan 震旦学院, mot à mot « le tonnerre du lever de soleil »), est une institution catholique française fondée en 1903 à Shanghai par un Jésuite chinois, Joseph Ma Xiangbo (马相伯), destinée à contribuer à la modernisation de la Chine. En 1907 la Société de Jésus fit l’acquisition d’un terrain à proximité de l’Université Auroré sur lequel elle édifica l’Hôpital Sainte Marie, rebaptisé ultérieurement Hôpital Guangci (广慈医院, mot à mot, « Hôpital de la Grande Miséricorde »). Cet hôpital se transforma en centre d’enseignement pour les élèves de l’Académie Auroré. En 1917 l’Académie fut promue au rang d’université, la prestigieuse Université Auroré, et devint une pépinière de médecins, d’infirmières, et de techniciens médicaux pour les hôpitaux catholiques de Chine. Une succession de doyens jésuites français en fit un phare de la médecine et de la langue françaises où se côtoyaient étudiants français et chinois. En 1952, toutes les institutions éducatives étrangères en Chine passèrent sous direction chinoise et l’Université Auroré fusonna avec l’Université Fudan (复旦大学), tandis que son école de médecine fut intégrée à l’École de Médecine de l’Université de Shanghai No. 2. L’Hôpital Guangci, quant à lui, fut renommé Hôpital Ruijin (瑞金医院), pour devenir un des centres hospitalo-universitaires de pointe de la Chine. Au cours des années 1980, l’École de Médecine de l’Université de Shanghai No. 2 renoua avec son passé en proposant un enseignement de 7 ans de médecine en langue française et en établissant un programme très dynamique d’échanges entre la Chine et la France à tous les niveaux. Nul n’illustre mieux le succès de cette entreprise que l’actuel Ministre de la santé chinoise, le Professeur Chen Zhu (陈竺), hématologue de renommée mondiale, dont le brillant parcours médical s’est effectué tant à l’École de Médecine de l’Université de Shanghai N° 2 qu’à la Faculté de Médecine Paris VII. De nos jours, un nombre croissant de médecins et scientifiques français se rendent à l’Hôpital Ruijin non seulement pour enseigner, mais pour apprendre. Les espoirs placés par le fondateur jésuite Ma Xianbo dans son Académie se trouvent ainsi pleinement réalisés.
The foreign concessions

It has often been said that the presence of the foreign nations who were granted settlements and concessions in Shanghai by the 1842 Treaty of Nanjing contributed to jumpstart its transformation, within less than a century, from a fishing village to one of Asia’s greatest metropolises. Yet with its two to three hundred thousand inhabitants, mid-19th century Shanghai was already a thriving port, whose junks sailed up and down the coast and across the East China Sea to Japan. However, the opening of the foreign concessions did prompt Chinese and Westerners alike to pursue a whole host of activities that propelled Shanghai into the 20th century.

Shanghai occupied a strategic position at the mouth of the Yangzi River, which the foreign nations were quick to perceive as ideal for trade. In 1845, Intendant Gong, a well-read Confucian, drew up Land Regulations, which allocated the representatives of the French, British, and Americans agricultural land and swamps north of the fortified town (several buildings of which still exist, even though drastically renovated, in what is known as the “Old City,” surrounded by a circular avenue that has replaced the walls). In 1949, an agreement was drafted by the TaoTai (city official appointed by the Qing dynasty) Lin-Kuei, who allowed the French to settle on land situated between the walls of the Chinese town and the Yangjingbang Creek.

Shanghai, one of the world’s largest and most vibrant metropolises, with a population of over 20 million people, boasts a skyline that since the 1990s has undergone such dramatic changes that frequent travelers to the city are constantly disoriented by the disappearance of old landmarks and the practically overnight springing up of new skyscrapers vying with each other for world records of height, avant-gardism, environmental sophistication, and sheer breathtaking beauty. Probably the most symbolic example is the “Pudong New Area,” built on former farmland on the east side of the Huangpu River, which has become China’s new financial hub, with its famous Shanghai World Financial Center (492 meters), Oriental Pearl Tower, with its 11 spheres, and Jin Mao building housing the Grand Hyatt Hotel on the 36 uppermost of its 88 floors. Although sizeable areas of Old Shanghai have been irretrievably lost in the process, much has been done to preserve major vestiges of the past. Most conspicuous among the escapes of the wrecking ball are two historical districts that bear the architectural stamp of the foreign nations that were granted extraterritorial settlements and concessions in the wake of the Nanjing Treaty, in 1842, which opened various ports, including that of Shanghai, to international trade. One is the “ Bund,” which runs along one mile of the western bank of the Huangpu River and is still lined by over 50 former British, Dutch, French, German, Japanese, Russian, and US banks, trading houses, consulates, etc, of various styles. The other is the “French Concession,” where plane tree–lined streets featuring many typically French mansions have been carefully preserved, and where a whiff of the “Paris of the Orient,” as the district was called, still pervades the air.
During the turmoil of the Taiping Rebellion (1851-1864), notably when the Small Swords Society occupied the Chinese city in 1853, over 20,000 locals sought safety in the concessions, creating a social mix that transformed the concessions into Sino-Western towns. One- or two-storey lilong houses (li means communities and long signifies lanes, whence lane-and-community–based urban dwellings) were put up everywhere and rented to local Chinese. Because of the increased demand for administrative services resulting from this sudden population upsurge, the British, French, and American consuls together drew up municipal regulations in 1854, authorizing the foreign communities, represented by property owners, to run the concessions. The resulting Shanghai Municipal Council fixed taxes, for foreigners and Chinese, to fund urban projects and set up a police force. The French had misgivings about this creation of a single administration, and in 1861 refused to ratify the new municipal regulations. The French Concession then went it alone with an independent municipal council placed under the authority of the consul, in other words, the Ministry of Foreign Affairs in Paris. In 1863, the British and American concessions fused and took the name of the Shanghai International Settlement. This division of Shanghai and the concomitant existence of rival authorities, jealously guarding their own prerogatives, contributed to the emergence of a unique social and political space within the urban center destined to become the most influential metropolis of Asia in the years before World War II.

By the dawn of the 20th century, Western trading interests had spread beyond Shanghai through a network of towns and ports around the coast and upcountry along the Yangzi River. Shanghai naturally was the prime beneficiary of this growth. Through its port passed over half of all Chinese imports and exports. Trading firms and transport companies abounded and expansion in international and waterborne trade opened up new markets. Driven mainly by private business, stores and artisans’ workshops sprang up across the city: the 1909 Shanghai guide listed 430 shops; the number had risen to 520 in 1910, and tripled by 1914.

The effectiveness of international trade was much dependent on rapid access to information. With the advent of the telegraph (1865), information from London or Paris could reach China in a few hours rather than thirty days, and the Chinese quickly seized the opportunities offered by this new means of communication.

The building of new roads to convey merchandise to Shanghai’s warehouses also stimulated growth, as did the rail link between Shanghai and Nanking (1902), which heralded the building of tramways in the concessions and in the Chinese town.

The opening of the Suez Canal in 1869 shortened to two months or less the sea voyage to China, lent new impetus to the freight between Europe and Asia, and spurred develop-
opment of newer steamships, since the narrow waterway was difficult for clippers to navigate. Shanghai was upgraded to one of the world’s foremost ports thanks to dredging work by the Chinese administration from 1906 to 1910, with the help of foreign engineers.

**The French Concession**

When he arrived in Shanghai in early 1848 as the first French Consul, Charles de Montigny’s mission was to look after the interests of the French community, at this time little more than a handful of tradesmen and missionaries. Anxious to fix the geographical limits of the French Concession, de Montigny negotiated an area of 66 hectares, bordered to the east by the Huangpu River, and to the north by the much larger British Concession (199 hectares).

**Public works**

From the creation of the municipal council (1862), a series of public works took shape. One of the first projects was the building of new roads, followed by work on drainage, paving, and sewers, funded by mandatory contributions from property owners. From 1887, the French Concession was the first to start a land register in order to raise local and land taxes. Constructions were regulated and subject to approval by the municipal council. Perspectives were defined, which doesn’t seem to have been the case for the International Settlement, whence the difficulty of joint realization of infrastructure work, such as the filling in of the Yangjingbang Creek, which had become an open sewer. Common projects were, nonetheless, completed, such as the slaughterhouse, the cemetery, and a fire department water tank, and traffic and police rules were decided jointly.

Created in 1906, the French Shanghai tram company fared well and by the 1930s had 100 trams, 60 buses, and 38 trolleybuses, and supplied countless households with electricity and water. Although its salaries were somewhat lower than those of its rivals, the company was forward-looking and offered better welfare benefits: housing, relief funds, cost of hospitalization and treatment, school funds.

**Banking**

The arrival in Shanghai of the *Comptoir National d’Escompte de Paris* in 1860 launched French banking in China. When it opened its Shanghai branch in 1898, the *Banque de l’Indochine* became the leading French bank in China and led efforts to counter the hegemony of the British Hongkong and Shanghai Banking Company Limited (HSBC), one of the oldest banking groups ever founded. Back home in France, silk production could not meet the demand for luxury silk goods, long craved by the French nobility and later by the middle classes that emerged during the industrial revolution. The French State therefore decided to buy directly from China, and from 1848 to 1873 fifteen French silk merchants set up in Shanghai. Around 1900, Shanghai had sixteen silk mills, and the industry attracted more foreign investors than any other.

**Public health and welfare**

Public health issues in Shanghai were addressed on the arrival of Westerners, no doubt impelled by the dangers of unwholesome surroundings (swamps, canals) and a climate conducive to contagion. Improving public health was also a way for Westerners to win hearts and minds in the Chinese community. In 1844,
English missionaries set up the Shanghai Hospital, the first in the foreign concessions, and a few years later French missionaries opened the General Shanghai Hospital and American missionaries the Hongkew Hospital. As modern medicine was gradually put in place, health care establishments multiplied on the initiative of foreign and Chinese doctors. Shanghai soon had the highest concentration of doctors in the land, particularly those trained overseas (22%) or in foreign universities in China. In the 1930s, 1300 physicians trained in Western medicine and 5600 doctors of Chinese medicine tended the sick of Shanghai. No other city in China could boast such a health care infrastructure.

**French schools**
The French Jesuits founded the Collège Saint Ignace, the first Catholic school in China, in 1847, and ten years later it had 82 pupils, who studied Chinese characters, French, music, and drawing. Saint Ignatius Cathedral was built between 1905 and 1910. Children of Christian families received both a religious education and literary training to enable them to sit the exams for the Chinese baccalaureate. In 1886, the French municipality created and financed the Franco-Chinese municipal school, the first of its kind. Teaching was entrusted to the Jesuits and then to the Marist Brothers. Young Chinese from the working classes received instruction and often went on to work in business, the administration, or the railways. Chinese pupils on scholarships were sent to France to achieve mastery of French language and culture so that they would create businesses on their return to their homeland. In addition to the cathedral, the French Jesuits also built orphanages, monasteries, schools, libraries, and an observatory.

**Aurore University**
Ma Xiangbo, a Jesuit catholic priest and man of letters, founded Aurore University, the jewel of French educational establishments in China, in 1902. This Franco-Chinese institution included departments of literature, philosophy, mathematics, and natural sciences, to which were added in 1914 faculties of arts-law, civil engineering, and medicine. Upon completion of a six-year course, Aurore medical graduates were eligible to enter the fifth year of medical school at Paris University. After a civil engineering degree (five years), awarded on presentation of a technical project, a graduate could enter the National College of Electrical Engineering in Paris.

Following differences of opinion with the French Fathers, Ma Xiangbo in 1905 created Fudan University, whose diplomas were recognized by both the French and Chinese governments, and which admitted its first female students in 1937.

**The arts**
The emergence of a Chinese bourgeoisie in Shanghai led to the creation of a school of guohua painting that produced great painters and calligraphers at the end of the Qing Dynasty (1644-1912) and during the Republic (1912-1949). The Jesuits at Zikawei ran an orphanage, a printing works, the site of China’s first lithographic press (1876), and a center of Western arts and crafts, where Chinese artists could take classes in drawing and anatomy, thus breaking with their artistic tradition. Zhou Xiang, a functionary of the tenth Qing Emperor, who had spent several years in France, established a school that pioneered Occidentalism in Shanghai, particularly in the illustrated press. In 1912 one of its students, Liu Haisu, founded in the French Concession the veritable forerunner of modern schools of fine arts, a mixed academy whose revolutionary teaching methods drew inspiration from those of the Parisian academies, where thirty or more future Chinese masters studied fine arts between 1910 and 1930. Sartorial inspiration too was to be seen in the concession’s “little Montmartre” where, after the manner of French artists, floppy neckties were all the rage.

Lin Fengmian, studied in Dijon, Paris, and Berlin from 1918 to 1926, married the French sculptress Alice Vattant, and on his return to China was appointed director of the Peking Institute of the Arts. Later he ran the new National Academy of Art in Hangzhou, near Shanghai, where, influenced by impression-
ism, he taught oil painting. This prestigious school became the center of Chinese modernism from which other remarkable painters were later to emerge, notably the Frenchmen Zao Wou-ki (who exhibited in 2008 at the Bibliothèque Nationale de Paris) and Chu Teh-Chun, and the Americans Chao Chung-Hsiang and Wu Guanzhong.

Pang Xunqin, who studied medicine at Aurore University and music in France, presented his canvasses at the 1925 Paris Exhibition. On his return to Shanghai in 1930, he created the Société des Deux Mondes, later known as “The Storm Society,” which organized four milestone exhibitions in the French Concession. André Breton’s Surrealist Manifesto was translated into Chinese in 1935 on the occasion of the first surrealist exhibition organized by the French Concession for Independent Chinese Artists.

**Architectural styles**

In the 1920s, along the Bund, the urban waterfront on the Huangpu River, foreign wealth and power were incarnate in elegant, even vainglorious, monumental buildings. This craze for ever higher edifices was not shared by the French, whose architectural legacy can be seen to this day in fine buildings like the Chung Wai Bank, as well as the Gascogne, the Béarn, and the Picardie, all three classified as historic buildings by the Shanghai Municipality, whose Art Deco charm, like that of the Normandie (1937-1938), has not faded with the passing of the years.

**Cultural life and leisure activities**

The foreign presence in Shanghai galvanized the newspaper business and publishing. First published in 1850, the British weekly North China Herald included a supplement in Chinese from 1861, was renamed three years later as the North China Daily News, and became the most influential foreign newspaper of its time. Le Journal de Shanghai catered for the French community, and Shen Bao, first published in 1872 and written entirely in Chinese, was soon the most powerful newspaper in China and remained so until 1949. In the concessions there were 2487 bookstores in 1938, compared with 136 in Peking and 40 in Nanking. It therefore comes as no surprise to learn that between 1920 and 1945 Shanghai counted the largest number of intellectuals of any city in China.

Shanghai had long enjoyed a nightlife worthy of a port and commercial hub, and by the 1920s its range of distractions was unrivaled in China. From 1912, the Grand Monde, one of the main centers of entertainment, hosted a panoply of distractions—theater, cafés, restaurants, gaming rooms, and cinema (by 1940 there were 57 film theaters in Shanghai). Gambling, one of the great Chinese passions, flourished in the concessions despite its prohibition under the Qing Dynasty and then under the Republic. The social life of Westerners in the concessions centered on their clubs. Each nationality had its own and the archetype

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“Paris of the Orient”: The Shanghai French Concession (1849-1946) – Camus

A view of the famous, still extant Bund (Huangpo River Embankment) and its European-style buildings. © Bettmann/Corbis.

Leafy archway of plane trees in today’s French Concession in Shanghai. “Quiet Streets,” photo by Alan Levine. With kind permission.
was the British residents’ Shanghai Club, famous for its marbles, paneling, and bar of over 30 meters—the “longest in the world.” The price of admission though was beyond the means of ordinary residents. The French Sports Club, with its fine ballroom and covered swimming pool, was the most popular venue.

The curtain falls... and rises again

In the 1940s, after close to a century, the end of the concessions drew near. When the Imperial Japanese Army occupied Shanghai in 1941, hundreds of thousands of displaced Chinese poured into the concessions, which became foreign islands in a sea of invading Japanese forces. The Sino-British Friendship Treaty of February 1943 returned the International Settlement to Chinese control, and on 30 July 1943 the Consul General Roland de Margerie officially handed over the keys of the French Concession to the Mayor of Shanghai.

Another 50 years later, what is left of the French Concession? Has anything survived the wrecking ball? The first thing that jumps to the eye is the plane trees that liberally line the streets and avenues of the former French district. This “greenery” in the modern city of steel, concrete, and glass is a welcome reminder of less hectic days and of the French way of life. Ironically what the French planted were “London planes,” but these trees immediately took the fancy of the Chinese who rechristened them “French planes.” The French Concession remained largely untouched until the 1980s, when Shanghai started its drive to develop into the megalopolis of today.

French names of streets have given way to Chinese names, many buildings have been torn down, and even the trees planted by the French on the former Avenue Joffre were removed—only for new trees to be hastily planted back to placate an angry neighborhood population. Plane trees have become so popular that they spill out in Shanghai beyond the bounds of the former French Concession and are even now found as roadside trees throughout China. Since the 2000s, the municipality of Shanghai has been taking active measures to preserve as much as possible of the vestiges of the French presence and is restoring old buildings and even some of the “lilongs” of the French Concession. The French Concession is, today, one of Shanghai’s major tourist attractions and the atmosphere of the “Paris of the Orient” is still palpable. But the story doesn’t stop there, and the “Touch of France” (to allude to the title of the cultural section of this journal) has come back in the form of a spate of French architects who have been or are being commissioned by the municipality of present-day Shanghai to leave their imprint on the city.

Jean-Marie Charpentier designed the Shanghai Grand Theater (“Opera”) situated near People’s Square in 1998; he landscaped a section of Nanjing Avenue (Nanjing Donglu) in 1999, which has become Shanghai’s bustling main pedestrian restaurant and shopping avenue, as well as the 4.5-km Century Avenue, the major thoroughfare destined to structure the 520 km² of the financial and commercial hub of Pudong and become Shanghai’s “Champs-Élysées” (2000); he built the General Motors Headquarters on the same Century Avenue (2004); the Shanghai Entry and Exit Visa Administration Bureau in Pudong (2005); and the Saint-Gobain (glass manufacturer) R&D Center, in the Minhang Development Zone (2007). Jean-Marie Charpentier has also been commissioned to rehabilitate an area of 50 000 m² in the French Concession to be completed in 2010. Paul Andreu designed Shanghai International Airport in 1999; the Oriental Arts Center in Pudong

“Paris of the Orient”: The Shanghai French Concession (1849-1946) – Camus
Jean-Marie Duthilleul designed the Shanghai South Railway Station in 2006. And to end this (nonexhaustive) list of major projects, Antoine Grumbach was commissioned in February 2008 to renovate 150,000 m² of Shanghai’s 19th-century historic center, on time for the Shanghai Expo 2010 World Fair.

Thus the French presence in Shanghai is not only a nostalgic thing of the past, but is even today actively contributing to shape the world’s most superlative city.

**Further Reading**

Instructions for authors

General instructions

- Manuscripts should be provided by e-mail (udit.siklosi@fr.netgrs.com) or by CD double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 90 characters (including spaces) double-spaced, 2.5-cm margins = a total of about 320 words per page.
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