Depression: isolated episodes or lifetime disorder?

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Major depressive disorder (MDD) is common, distressful, economically disadvantageous (occupational dysfunction includes absenteeism, decreased productivity, and unemployment), and potentially crippling financially for both family and society. Average onset is in the late 20s, but it can occur at any age. The most serious complications are suicide and other violent acts, but the potential impact is wide-ranging, from complicating recovery from physical illness to being a risk factor for events such as myocardial infarction. MDD has a lifetime prevalence of about 15%, but mood disorder rates range widely across the world, from 3.3% to 21.4% in the 14 countries (six less developed and eight developed) involved in the World Health Organization (WHO) World Mental Health Survey Initiative. According to the Global Burden of Disease Study (www.globalburden.org), conducted by the WHO, World Bank, and several universities (Harvard, Washington, Johns Hopkins & Queensland), depression alone accounts for over 12% of years lived with disability globally and is the third leading contributor to the disease burden, including all somatic illnesses.

The defining feature of a major depressive episode (MDE), according to the Diagnostic and Statistical Manual of Mental Disorders IVth Edition Text Revision (DSM IV TR), is a period of at least 2 weeks during which there is either depressed mood or loss of interest or pleasure in nearly all activities and at least four additional symptoms drawn from a list of seven others (sleep disturbances, changes of appetite or weight, psychomotor agitation or retardation, fatigue, guilt, diminished ability to concentrate, thoughts of death), which must persist for most of the day and nearly every day. Symptoms induce clinically significant distress and impairment and are not due to the effects of a substance or medical condition nor better explained by bereavement. The duration is variable, an untreated episode typically lasting 6 months or longer.

This “here and now” definition of depression is far from accounting for the complexity of depressive disorders and in particular for their long-term and even lifetime evolution. While a few people have just one MDE with full return to premorbid functioning (although residual symptoms and social impairment persist in 20% to 30%), over 60% of those having one such episode will proceed to another, at which point their illness will meet the criteria for recurrent depressive disorder (defined by the presence of two or more MDEs, each separated by at least 2 months). DSM IV provides different types of specific diagnostic features (severity, melancholic or catatonic features, postpartum onset, and seasonal pattern). One such specifier concerns the longitudinal course, which is heterogeneous. The risk of further episodes...
increases with each new episode: two MDE confers a 70% risk of a third, while three MDEs confer a 90% risk of a fourth. The many additional risk factors for recurrence include: incomplete remission, early age of onset, female gender, low socioeconomic and socioeducational level, personality disorder (neuroticism), psychiatric comorbidity, stressful life events, poor social support, inadequate coping, somatic disease, and iatrogenic treatment. However, the most important remain the number of past episodes and the presence of residual symptoms. Comorbidity is common in MDD (occurring in two thirds with DSM IV Axis I, one third with Axis II, and over half with Axis III).2

Depression tends to be not only recurrent, but also progressive in that episodes occur after shorter intervals of remission and with increasing severity and duration. A century ago, observing this progressive shortening of remission intervals and the decreasing role of psychosocial stressors in subsequent episodes, Emil Kraepelin wrote:

The attacks of depressive or manic-depressive illness begin not infrequently after the illness or death of near relatives. …In spite of the removal of the discharging cause, the attack follows its independent development. But, finally, the appearance of wholly similar attacks on wholly dissimilar occasions or quite without external occasion shows that even if there has been external influence, it must not be regarded as a necessary presupposition for the appearance of the attack."3

Many authors have since confirmed those clinical observations4-15 and systematic studies, such as the National Institute of Mental Health (NIMH) Collaborative Study on the Psychobiology of Depression, have provided data consistent with the fact that patients with “environment-sensitive” episodes have significantly fewer episodes than those with “autonomous” episodes.11 In the 1980s, Post and Ballenger proposed the kindling model to explain that, like kindled seizures, depressive episodes that are initially triggered by stressful life events begin to occur spontaneously.12 According to Post, both sensitization to stressors and episode sensitization occur and become encoded at the level of gene expression. In particular, stressors and the biochemical concomitants of the episodes themselves can induce the protooncogene c-fos and related factors, which then affect the expression of transmitters, receptors and neuropeptides that alter responsivity in a long-lasting fashion. Thus, both stressors and episodes may leave residual traces and vulnerabilities to further occurrences of affective illness [suggesting] that the biochemical and anatomical substrates underlying the affective disorders evolve over time as a function of recurrences, as does pharmacological responsivity.13

Thus, illness progression appears to involve not only psychological and clinical factors such as increasing treatment refractoriness (hence residual symptoms), cognitive dysfunction, social disability, and secondary comorbidity (eg, addiction), but also epigenetic changes.

A more recent hypothesis is that depression is toxic to cognitive function, as shown by reduced hippocampal volume and enduring memory impairment. Magnetic resonance imaging (MRI), functional MRI (fMRI) and positron emission tomography have all found hippocampal abnormalities in patients with recurrent depressive disorder or with chronic and/or severe depression. Reduction in hippocampal volume has been related to the number, intensity, and duration of depressive episodes and to the number of psychiatric hospitalizations, but has also been observed within a few years of depression onset.14,15 Hippocampal atrophy in recurrent depressive disorder may reflect the role of physiological stress as a pathological factor (hippocampal neurotoxicity by cortisol) mediated by a decrease in brain-derived neuroprotective factor (BDNF).16

As shown by the Pittsburgh Study of Maintenance Therapies in Recurrent Depression, the combination of antidepressant medication and cognitive-behavioral therapy gives the best result in MDE and must be maintained long term to prevent recurrence.17 Even an isolated depressive episode needs treatment in two phases: a curative 6- to 8-week phase and a continuation 4- to 6-month phase. The continuation phase becomes all the more important in treating recurrent depressive disorder, especially after the third recurrence. In addition to this clinical prophylactic intervention, appropriate treatment should aim to prevent or ameliorate both the increases in pathological factors and the erosion of adaptive factors that propel illness exacerbation and treatment resistance. As Post has argued:

This view of the sensitization and cross-sensitization among stressors, [depressive] episodes, and abused substances should lead to a fundamental reconceptualization of the recurrent affective disorders not as benign, isolated episodes of “mental” illness, but as severe, potentially progressive and lethal medical disorders of brain and body that deserve careful lifelong monitoring and treatment.18

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**Selected Abbreviations and Acronyms**

- **BDNF** brain-derived neuroprotective factor
- **CBT** cognitive-behavioral therapy
- **DSM IV TR** Diagnostic and Statistical Manual of Mental Disorders IVth Edition Text Revision
- **fMRI** functional magnetic resonance imaging
- **MDD** major depressive disorder
- **MDE** major depressive episode
- **MRI** magnetic resonance imaging
- **WHO** World Health Organization
References


Keywords: depressive episode; depressive disorder; epidemiology; recurrence; hippocampus
Le trouble dépressif majeur (TDM) est une affection fréquente, à l’origine d’une détresse profonde, d’une charge économique importante (perturbations professionnelles comprenant absentéisme, diminution de la productivité et chômage) et d’un impact financier potentiellement lourd pour la famille et la société. L’âge moyen de survenue se situe entre 25 et 30 ans, mais il peut se déclencher à tout moment. Les complications les plus graves sont le suicide et les autres actes violents, mais les conséquences potentielles sont variées, car il peut aussi bien compliquer la récupération d’une maladie physique que constituer un facteur de risque pour des événements comme un infarctus du myocarde. Le TDM montre une prévalence de 15 % sur l’ensemble de la vie, mais la fréquence des troubles de l’humeur varie fortement à travers le monde, de 3,3 % à 21,4 % dans les 14 pays (six pays en voie de développement et huit pays développés) participant à l’Initiative Mondiale pour une Enquête sur la Santé Mentale (World Mental Health Survey Initiative) de l’Organisation Mondiale de la Santé (OMS). Selon l’Étude sur la Charge Globale des Maladies (Global Burden of Disease Study) (www.globalburden.org), menée par l’OMS, la Banque Mondiale et plusieurs universités (Harvard, Washington, Johns Hopkins et Queensland), la dépression seule représente plus de 12 % d’années de vie affectées par une incapacité d’une manière générale, et se range au troisième rang dans la charge pathologique globale, qui comporte toutes les maladies somatiques.

La caractéristique définissant un épisode dépressif majeur (EDM), selon le Manuel Diagnostique et Statistique des Troubles Mentaux IV, Édition Révisée (Diagnostic and Statistical Manual of Mental Disorders IV Edition Text Revision, DSM IV TR), est une période d’au moins deux semaines au cours de laquelle le patient présente soit une humeur déprimée soit une perte d’intérêt ou de plaisir pour pratiquement toutes les activités, et au moins quatre autres symptômes d’une liste comprenant sept autres (troubles du sommeil, changement de l’appétit ou du poids, agitation ou retard psychomoteur, fatigue, culpabilité, diminution de la capacité de concentration, pensées de mort), qui doivent persister presque tous les jours et pendant la majeure partie de la journée. Les symptômes induisent une détresse et des altérations cliniquement significatives, et ne sont pas dus aux effets d’une substance ou d’une affection médicale et ne peuvent pas non plus être expliqués par un deuil. La durée est variable, un épisode non traité durant généralement au moins six mois.

Cette définition immédiate de la dépression est loin de refléter la complexité des troubles dépressifs, en particulier dans leur évolution à long terme, parfois sur toute la durée de la vie. Si quelques personnes ne souffrent que d’un seul EDM et revien-
La dépression a tendance non seulement à récidiver, mais également à évoluer dans la mesure où les crises surviennent après des épisodes de rémission de plus en plus courts, et avec une sévérité et une durée aggravées. Il y a un siècle, après des épisodes de rémission de plus en plus courts, et très fréquents, les épisodes dépressifs initialement provoqués par une cause externe montrent que, même s’il existe une influence physiologique comme facteur pathologique (neurotoxicité hippocampique), l’IRM a permis d’obtenir des données confirmant que les patients présentant des épisodes « en relation avec l’environnement » présentaient un nombre significativement inférieur d’épisodes à ceux qui développent des épisodes « autonomes ».11 Dans les années 1980, Post et Ballenger ont proposé un modèle de type « embrasement » pour expliquer que, comme les crises convulsives déclenchées, les épisodes dépressifs initialement provoqués par des événements stressants commencent à survenir spontanément.12 Selon Post, la sensibilisation aux facteurs de stress et la sensibilisation aux épisodes surviennent et deviennent encodées au niveau de l’expression génique. En particulier, les facteurs de stress et les paramètres biochimiques des épisodes eux-mêmes peuvent induire le proto-oncogène c-fos et des facteurs apparaissant à l’occasion de crises compliquées, qui affectent ensuite l’expression des transmetteurs, des récepteurs et des neuropeptides, alléger la facture de réponse à long terme. Par conséquent, les facteurs de stress et les épisodes peuvent laisser des traces résiduelles et une vulnérabilité à la survenue d’autres épisodes de la pathologie affective (suggérant que les substrats biochimiques et anatomo-morphologiques sous-jacents aux troubles affectifs évoluent avec le temps en fonction des récidives, comme la réactivité pharmacologique).13

La progression de la maladie semble donc comporter non seulement des facteurs psychologiques et cliniques, notamment des épisodes de plus en plus réfractaires au traitement (laissant par conséquent des symptômes residuals), un dysfonctionnement cognitif, une incapacité sociale et des comorbidités secondaires (par exemple, accoutumance), mais également des changements épigénétiques.

Une hypothèse plus récente a proposé que la dépression pourrait exercer une activité toxique sur la fonction cognitive, se manifestant par une réduction du volume de l’hippocampe et provoquant des troubles de mémoire persistants. L’image par résonance magnétique nucléaire (IRM), l’IRM fonctionnelle (IRFM) et la tomographie par émission de positons ont toutes mis en évidence des anomalies de l’hippocampe chez les patients présentant des troubles dépressifs récidivants ou une dépression chronique et/ou sévère. Une réduction du volume hippocampique a été liée au nombre, à l’intensité et à la durée des épisodes dépressifs, ainsi qu’au nombre des hospitalisations psychiatriques, mais a également été observée quelques années après le déclenchement d’une dépression.14,15 L’atrophi que hippocampique observée dans le trouble dépressif récidivant pourrait refléter le rôle du stress physiologique comme facteur pathologique (neurotoxicité hippocampique du cortisol) assuré par la médiation d’une diminution du facteur neuroprotecteur BNDF (brain-derived neuroprotective factor).16

Comme l’a montré l’Étude de Pittsburgh sur les Traitements d’Entretien dans le Trouble Dépressif Récidivant (Pittsburgh Study of Maintenance Therapies in Recurrent Depression), l’association d’un antidépresseur et d’un traitement cognitivo-comportemental donne les meilleurs résultats dans les EDM, et doit être maintenue à long terme pour prévenir les récidives.17 Même un épisode dépressif isolé doit recevoir un traitement en deux phases : une phase curative de 6 à 8 se-
maines et une phase de continuation de 4 à 6 mois. La phase de continuation revêt un caractère essentiel dans le traitement du trouble dépressif récidivant, en particulier après la troisième récidive. Outre cette intervention clinique prophylactique, le traitement approprié doit viser à prévenir ou améliorer l’augmentation des facteurs pathologiques et l’érosion des facteurs adaptatifs, qui favorisent l’exacerbation de la maladie et la résistance au traitement. Comme Post l’a indiqué :
Cultural aspects of depression as a diagnostic entity: historical perspective

by M. C. Kastrup, Denmark

Globalization and increasing pluralism require psychiatrists to evaluate the impact of cultural factors on depressive disorders. Modern classification systems should pay due attention to culture-specific factors, and systematic, operationalized appraisals are needed in order to assess cultural elements. In the Diagnostic and Statistical Manual of Mental Disorders IVth Edition (DSM-IV), the Cultural Formulation was introduced, in order to provide an operational approach of the cultural perspective and allow patients to reflect cultural elements in their narratives. Prevailing classification systems are still criticized as reflecting Western concepts and not paying sufficient attention to the symptomatology of patients of non-Western backgrounds. Depression has a multifaceted etiology, and migrants run a particular risk, in part due to the migratory process itself. One should therefore distinguish culture-specific issues and migration-specific issues. The lifetime risk for a major depression is as high as 12% to 16%. The World Health Organization has predicted that in 2020 depression will be the second most important cause of disability. Culture influences depressive symptomatology, explanatory models, help-seeking behavior, and societal response. Furthermore, treatment tends to differ according to culture and so does the treatment gap.

Medicographia. 2011;33:119-124 (see French abstract on page 124)

With increasing globalization, mental health professionals are being confronted with decisions related to culture-specific aspects of diagnosis, validity of diagnostic entities, and variability of symptoms. It is important to be able to evaluate the role of culture in explaining differences in symptom manifestation and to be aware of the interaction between culture and depressive symptomatology when assessing a depressed patient. Assessing depressive disorders in persons from a variety of cultural backgrounds is becoming part of routine clinical work in many mental health settings. This paper examines issues related to cultural aspects of depression, with particular focus on diagnosis.

Diagnostic considerations

Classification systems are affected by changes in our professional knowledge and orientation, by the actual situation in society, and even by political ideologies. Tseng further points out that hitherto it has been easier for Western psychiatrists to adapt to classification systems developed in the West than it is for non-Western psychiatrists, who experience a disparity between their actual practice of psychiatry and...
Cultural aspects of depression as a diagnostic entity: historical perspective – Kastrup

Depression: Isolated Episodes or Lifetime Disorder?

OUTLINE FOR CULTURAL FORMULATION IN DSM-IV

◆ Cultural identity of the individual. Note the individual’s ethnic or cultural reference groups. For immigrants and ethnic minorities, note separately the degree of involvement both with the culture of origin and the host culture. Also note language abilities, use, and preference (including multilingualism).

◆ Cultural explanation of the individual’s illness. The following may be identified: the predominant idioms of distress through which symptoms or the need for social support are communicated (eg, “nerves,” possessing spirits, somatic complaints, inexplicable misfortune), the meaning and perceived severity of the individual’s symptoms in relation to norms of the cultural reference group, any local illness category used by the individual’s family and community to identify the condition (see “Glossary of Culture-Bound Syndromes” below), the perceived causes or explanatory models that the individual and the reference group use to explain the illness and current preferences for and past experiences with professional and popular uses of care.

◆ Cultural factors related to psychosocial environment and levels of functioning. Note culturally relevant interpretations of social stressors, available social supports, and levels of functioning and disability. This would include stresses in the local social environment and the role of religion and kin networks in providing emotional, instrumental, and informational support.

◆ Cultural elements of the relationship between the individual and the clinician. Indicate differences in culture and social status between the individual and the clinician and problems that these differences may cause in diagnosis and treatment (eg, difficulty in communicating in the individual’s first language, in eliciting symptoms or understanding their cultural significance, in negotiating an appropriate relationship or level of intimacy, in determining whether a behavior is normative or pathological).

◆ Overall cultural assessment for diagnosis and care. The formulation concludes with a discussion of how cultural considerations specifically influence comprehensive diagnosis and care.


In the Diagnostic and Statistical Manual of Mental Disorders IVth Edition (DSM-IV), Cultural Formulation was introduced to apply a cultural perspective to the clinical evaluation and to allow an operational approach and an individual assessment. This can be seen as a significant step toward a cultural-competent and cultural-sensitive assessment of mental disorders Table 1. Using the Cultural Formulation to assess a depressive episode enables the patient to provide a narrative of all components reflecting cultural elements. It offers a larger scope than purely diagnostic evaluation by encompassing aspects international classification systems. The diagnosis of depression has undergone major changes over time. In spite of the fact that melancholia and depression have been described for many centuries, the classification of depression has given rise to extensive debate. The very concept of depression is not universally accepted and, historically, many non-Western societies have consistently reported lower prevalences of depression than Western societies. Variations in diagnostic categories over time—including entities like endogenous versus reactive depression; psychotic versus neurotic depression; depression versus dysthymia—have also made comparisons across cultures or time difficult. From the point of view of research, the classification of depression is controversial. In many non-Western languages, there is no corresponding word for “depression” in spite of the fact that lowered mood is a universally encountered phenomenon. Furthermore, methodological differences, such as variations in study samples; differences in methodologies in clinical assessments, or lack of culturally validated assessment instruments, contribute to transcultural variability in depression.

Confronted with a depressive patient of similar cultural background as their own, many clinicians may fail to recognize the prominent role of the cultural element and tend to underestimate its importance. In contrast, when dealing with a depressed patient from another cultural background, cultural differences may become obstacles for the clinician and thus mask the depressive process.

The concept “category fallacy” was introduced to illustrate a fundamental error in transcultural diagnostics. When psychiatrists reject “non-Western” disease categories as being culture-specific, they so-to-speak impose their own cultural categories on the “non-Western” categories in the false conviction that these are neutral and culture-independent.

Several proposals have been made to overcome these diagnostic difficulties. One would be to introduce an independent cultural axis in the diagnostic systems; another would be to include culture-bound syndromes as part of the nosological entities.

As a result of expanding migratory population movements, it is increasingly recognized that culture-specific factors related to modern societal realities should be taken into account by international classification systems. Yet, culture does not have a prominent explicit place in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), even though the development of ICD-10 did include field trials in a number of countries worldwide.

Selected Abbreviations and Acronyms

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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>DALYs</td>
<td>disability-adjusted life years</td>
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<tr>
<td>PHC</td>
<td>primary health care</td>
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<tr>
<td>YLDs</td>
<td>years lived with disability</td>
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of the patients’ social universe, personal interpretations, explanatory reflections, and attitudes toward help-seeking. A comprehensive biographical history, taking into account the patient’s cultural reference group and identity, as well as stressors related to migration and acculturation, enables better understanding of the depressive disease process and of its impact on patients and their relatives. Yet despite this innovation, objections are raised that classification systems nevertheless continue to reflect Western concepts and values and cannot be used uncritically in patients of other cultural backgrounds.

When diagnosing depression be aware of:
- Differences in explanatory models
- Unwillingness by the patient to disclose all symptoms
- Somatic presentations of symptoms and somatic comorbidity
- Variation of clinical features across cultures
- Barriers between doctor and patient—eg, linguistic, racial
- Insufficient probing of symptoms and history by the clinician
- Doctor’s attitude and familiarity with depression

Table II. Guidelines for diagnosis of depression by a clinician from another culture than the patient’s.

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<th>Condition</th>
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<td>Doctor’s attitude and familiarity with depression</td>
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Epidemiology
Historically, it has been a frequently held belief that depression, in developing countries, in particular in Africa and Asia, is an infrequent illness compared with Western countries, and suicides due to depressive illness were thought to be extremely rare in non-Western countries. Investigations carried out by the World Health Organization (WHO) have demonstrated today that depressive disorders occur in all cultures. Cross-cultural comparisons of depressive disorders, eg, the WHO study following a cohort with standardized assessments in 5 different countries, show similarities in symptoms, such as lowered mood, sleep disorders, lack of energy, and concentration difficulties. Depression today is a huge and increasing public health concern on a global level. Neuropsychiatric disorders contribute 31.7% of all YLDs (years lived with disability) according to WHO, with unipolar depression ranking highest (11.8%). Among the ten most important diseases measured by YLDs, psychiatric conditions make up four, among which unipolar depression. Around 360 million persons throughout the world suffer from mood disorders. Furthermore, depressive disorders are the fourth most important contributor to the global burden of disease, and in adults aged 15 to 44 years, they are the leading cause of DALYs (disability-adjusted life years) lost worldwide. As persons under 45 years run a greater risk of depression, persons are affected during their most productive years of life, in all cultural settings. About 5% to 10% of persons at any given time are suffering from identifiable depression that requires psychiatric/psychosocial intervention, while the lifetime risk for major depression is 12% to 16%. WHO has predicted that in 2020 depression will be the second most important cause of disability. In the European Region, the prevalence of major depression and bipolar disorders totals 21 million. It is well documented that women run a greater risk in most cultures: overall, women have a 1.5- to 2-times higher risk of suffering from depression compared with men. In the Cross-National Collaborative Group, women in all countries had a higher prevalence with a female: male ratio varying from 1.6 in Lebanon to 3.1 in West Germany. Possible explanations for these differences include the multiple roles women have as homemakers, professionals, wives, and mothers.

The rate of depression does not vary significantly with ethnicity. Socioeconomic or educational differences may contribute to differences between ethnic groups, but the differences disappear to a large extent when controlled for these. The burden of depression (Figure 1, page 122) is relatively smaller in poorer regions of the world, eg, depression represents 1.2% of the disease burden in Africa compared with 8.9% in high-income countries, but depression is predicted to become a leading cause of disease burden in developing countries as well. It has been suggested that differences in the prevalence of depression may reflect dysfunctionality of a changing culture.

Primary health care
General practitioners often diagnose depressive disorders. A WHO study of 15 primary care centers reported that 11.7% of patients presenting in a primary health care (PHC) setting had depression, but the fact that the psychiatric problem was generally not the presenting complaint meant that the depression risked going unidentified. The frequency of depression in the community was measured by the WHO in its General Health Care Study including 14 countries around the world. The prevalence of current depression was found to vary from 2.6% in Nagasaki to 16.9% in Manchester and 29.5% in Santiago. The range in frequency was interpreted as: (i) reflecting true differences in prevalence; (ii) cultural variations in disease concept; (iii) differences in help-seeking behavior; (iv) or differences in demographic characteristics.
Provoking factors

Depression is acknowledged to be a disorder with a multifaceted etiology. Depressive syndromes are very common in migrants, and up to half of all migrants in the US may have clinical depression.25 The very process of migration itself may be partly responsible for the risk of emergence of stress-related disorders. A wide range of provoking factors may contribute to an episode in minority ethnic groups. These include: premigratory stressors; personality; physical health problems; as well as postmigratory stressful living conditions; discrimination; socioeconomic adversities; cultural conflicts; personal losses related to migration, etc (Table III).

In addition, persons coming from traditional, sociocentric, societies, who migrate to a Western country with a more egocentric type of society, may feel alienated, which makes adjustment more difficult and results in an increased risk of mental health problems.27

Migration is thus a highly complex experience comprising a range of processes, influences, and conditions that may affect health and illness.29 At the same time, migration and the cultural change from a traditional, more community-centered, society to a modern, individualistic society, can lead to decompensation of coping mechanisms and emergence of depression. As the above shows, migration can trigger mental disorders when the protective function of the original culture is missing.29

Cultural dimensions

WHO reports indicate considerable cross-cultural similarities in depressive symptomatology, with symptoms such as low mood, lack of joy, anxiety, lack of energy and interest in surroundings evidenced in most cultures.30 However, cross-cultural differences do exist: for example, feelings of guilt are one of the major symptoms of depression in Western countries even though they are not specific and can be observed in many other cultures, albeit with far lesser frequency. Thus, a WHO study reported the highest frequency of feelings of guilt in Swiss patients and the lowest in Iranian patients, while somatic complaints were more common in the latter.31

In non-Western patients delusions often have themes like physical health, or religion, and are not, as in Western patients, constructed around guilt and inferiority.2 Due to the absence of the dualistic body-soul distinction prevalent in Western cultures, patients in some non-Western countries often have narratives that contain metaphors of body functions when describing their emotional state rather than psycho-

Table III. Diagnosis of depression in migrants.

logical terms. Nevertheless, somatization as a sense of bodily discomfort, or vegetative symptoms without any demonstrable organic cause, are part of depressive symptomatology in all cultures.

Culture may also influence the expression of depressive thoughts. The question of whether suicide is considered an acceptable strategy for solving conflicts in a seemingly hopeless situation is very culture-dependent, and vast differences in the traditions of suicide exist depending on which culture is considered. Depressive reactions following bereavements or as part of old age are in many cultures not seen as conditions requiring an intervention, but rather as part of normal life. Western psychiatrists should, however, also be aware of the fact that more severe depressive symptoms may be interpreted as normal reactions, thereby preventing the afflicted person from receiving adequate treatment.

Thus, the interaction between culture and depression should be borne in mind whenever interviewing a patient in whom a depressive episode is suspected. When diagnosing depression in persons of another ethnic origin it is important to distinguish culture-specific issues and migration-specific issues, as they may have a different impact on the intrapsychic conflict forming part of the migration process. The literature often fails to distinguish between the two and to indicate whether the increased vulnerability to depression is associated with the fact of being a migrant per se or with problems encountered in the host country due to cultural differences, or whether it is due to a combination of both (Table IV).

### Therapeutic aspects

When assessing the impact of culture on the treatment of depression, attention should be paid to the specific context. Clinicians trained in Western countries tend to focus only on the individual. But in many instances it may be of benefit to consider the depressed patient in a social context and take into account social values and role expectations. Clinicians from Western individualistic cultures sometimes falsely assume that cohesive family structures prevent personal growth and do not allow individualization, whereas in fact cohesive social patterns foster the development of a self-contained identity in accordance with one's role within a social hierarchical structure. Attitudes toward treatment tend to differ according to cultural context when comparing persons in their home country with the same ethnic groups having migrated to a Western country.

### Treatment gap

Overall, the increased focus on depression has failed to translate into a better situation for depressed persons, and there is still a significant lack of correlation between the disease's extent and the availability of adequate treatment (the so called treatment gap). This gap is highest in low- and middle-income countries, but even in Western Europe, the European Ministerial Report estimates the treatment gap at 45.4% for severe depression, while in low-income and middle-income countries only a small proportion of treated depressed patients are in fact adequately treated. Reasons for this treatment gap in many countries comprise the lack of trained staff, lack of resources, and stigma toward depression. Even in the US, it has been shown that the treatment gap varied considerably between ethnic groups.

In order to minimize the gap between the consequences of depression and the availability of treatment, research should focus on therapies that are practical and allow for the needs of the population in question. With the current focus on prevention, a cost-effective decrease in the current burden of depression is possible.

### References

Aspects culturels de la dépression comme entité diagnostique : perspective historique

Face à la mondialisation et au pluralisme croissant les psychiatres se doivent d’évaluer l’impact des facteurs culturels sur la dépression. Les classifications actuelles doivent prendre en compte les facteurs culturels spécifiques, et des méthodes opérationalisées systématiques doivent être mises en place pour évaluer les éléments culturels. L’Approche Culturelle (« Cultural Formulation ») a été introduite dans le DSM-IV (Diagnostic and Statistical Manual Disorders IVth Edition) pour présenter une démarche opérationnelle de la perspective culturelle et permettre aux patients d’introduire les éléments reflétant leur propre culture dans leurs récits de la maladie. Les méthodes de classification actuelles sont toujours critiquées comme traduisant des concepts occidentaux sans prêter suffisamment attention à la symptomatologie des patients non occidentaux. La dépression est d’étiologie multiple, et les migrants courent un risque particulier, dû en partie au processus migratoire lui-même. Il faudra donc distinguer les problèmes spécifiques de la culture de ceux spécifiques de la migration. Le risque sur la vie entière d’avoir une dépression majeure atteint jusqu’à 12 à 16 %. L’Organisation Mondiale de la Santé a prévu qu’en 2020 la dépression sera la deuxième cause la plus importante d’invalidité. La culture influe sur la symptomatologie dépressive, les modèles explicatifs, les comportements de demande d’aide, et sur la réponse de la société. Le traitement, quant à lui, diffère selon les cultures, de même que l’étendue du déficit de traitement (« treatment gap »).

Keywords: diagnosis; depression; culture; epidemiology; migration; globalization; gender
Relapse or recurrence in depression: why has the cutoff been set at 6 months?

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Classification into relapse or recurrence of a newly occurring depressive episode has important therapeutic implications. In the past, diverse outcome measures with arbitrary definitions have been used in antidepressant treatment trials. In an attempt to harmonize and standardize these definitions, a task force was set up by the MacArthur Foundation. This article summarizes the currently used definitions for response, remission, relapse, recurrence, continuation, and maintenance treatment, and discusses whether relapse is the consequence of incomplete remission. The two most important outcomes that are important in order to distinguish relapse from recurrence are the threshold for remission and the time spent in remission before recovery can be ascribed to a patient. For remission a 17-item Hamilton Depression Rating Scale (HAMD-17) threshold of below 7, and for recovery a time span of 6 months in remission seem to be now accepted by the research community. Recent research on remission thresholds, together with the role of unrecognized residual symptoms in the development of depressive disorder, are discussed. The “6-month” period for determining the end of an episode is explained and justified by two different approaches involving the length of the depressive episode and data from antidepressant discontinuation trials. To conclude, the limitations and pitfalls of both methods are discussed.

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Defining relapse or recurrence is directly dependent on the definition of the healthy, illness-free state commonly referred to as remission or recovery. Remission derives from the Latin word remittere (remisi, remissum), which literally translates as “to abate” or “to remit,” “to send back.” Clearly, in medical terms, the term remission relates to the former meaning, describing the “abatement” or the “decrease” of symptoms.

So from a linguistic point of view this would not necessarily imply absolute freedom of symptoms, but would rather describe an improvement in the course of illness. In the early days of depression research this has contributed to quite a few difficulties and much confusion regarding definitions of outcome terms like response, remission, and partial remission. This ultimately led to the paradox that one researcher’s definition of “remission” equated another researcher’s definition of “response.” In 1988, in an attempt to overcome these controversies, the MacArthur Foundation set up a task force led by Ellen Frank with the goal of achieving a con-
sensus in defining outcomes of clinical studies. This led to the current definition of “remission,” which, in its narrow medical sense, refers to the virtual absence of depressive symptoms. Terms like “recovery,” “relapse,” and “recurrence” were also precisely defined. Important therapeutic concepts relating to these outcomes, are “response,” and “acute, continuation, and maintenance therapy.” These terms have often been used quite arbitrarily in the past. After the publication of the consensus paper by Ellen Frank in 1991, the American College of Neuropsychopharmacology (ACNP) updated these recommendations by introducing small changes. In the wake of the MacArthur Foundation, several other groups were set up to standardize the definition of psychiatric terms such as bipolar disorder or schizophrenia. In the following, we briefly summarize the current concepts underlying the terms response, remission, recovery, relapse, and maintenance, before discussing in more detail some important aspects closely related to relapse and recurrence, as well as why the time span of 6 months was agreed upon.

Response
Response describes a gradual improvement during depression treatment and usually implies a treatment effect. Response is usually defined as a 50% improvement from baseline to end point on depression rating scales such as the 17-item Hamilton Depression Rating Scale (HAMD-17) or the Montgomery-Åsberg Depression Rating Scale (MADRS). Response tends to occur early on during the course of treatment (eg, after 2 weeks) and usually precedes remission as a precondition. It is the main categorical outcome parameter of short-term antidepressant trials. Thus, response occurs during the acute treatment phase of major depression.

Remission
As stated before, remission refers to a relatively short symptom-free period. Usually, remission is defined by a threshold on a depression rating scale. In contrast to response, remission is not necessarily related to any treatment. It can also occur spontaneously in patients without treatment. Michael Thase has shown that a threshold of equal to or below 7 on the HAMD-17 best distinguished healthy control persons from patients with major depression. Recently, this threshold was replicated in a large sample of naturalistically treated patients with major depression. In contrast to response, remission can occur with or without treatment. From a therapist’s perspective, remission is the starting point of continuation therapy with the primary goal of sustaining remission until recovery is achieved.

Recovery
The concept of recovery implies a prolonged period of remission. This period should be long enough so that a major depressive episode (MDE) is unlikely to occur in the near future. In other words, once a patient achieves recovery, many months of remission can be anticipated. In accordance with remission, recovery can be ascribed while the patient is either on or off treatment. From a theoretical point of view, recovery implies that the illness activity of the MDE is no longer present, but it is important to keep in mind that the underlying vulnerability may still be present. This also means that recovery refers only to the last episode and not to the affective disorder as a whole.

Thus, recovery is only lost if recurrence occurs. The ACNP Task Force recommends a time span of 4 months, while others have repeatedly used a 6-month duration to define recovery. The fact that a patient has recovered also raises the possibility for the treating clinician to consider discontinuing treatment, which is of course one of the most important clinical implications of recovery.
Relapse and recurrence
Both terms refer to the reappearance of a full-blown MDE. The essential distinction between both terms is the time at which each event occurs. According to the description by Frank et al, “relapse” is “a return of symptoms satisfying full syndrome criteria for an episode that occurs during a period of remission, but before recovery.” This again points to how critical the time criterion of recovery and the symptomatic threshold of remission are, as all other definitions are based upon them. As for “recurrence,” this is defined as “the appearance of a new episode of MDE, occurring during recovery.”

In summary, we not only discriminate remission and recovery, but also relapse as an early return or “fall back” into the initial MDE, and recurrence as a late return of the illness and as a development of a new depressive episode, unrelated to the prior, “cured” episode, respectively.

Continuation and maintenance therapy
These terms are closely connected with the terms relapse and recurrence. The goal of continuation therapy is to preserve the therapeutic success of the acute phase until recovery is achieved (Figure 1). In addition, clinicians should try to eliminate residual symptoms, restore social functioning, and prevent relapse of depression during continuation. The time span of the continuation therapy should have the length of the “natural course” of an MDE and is exactly the same time span that is used to define recovery.

In practice, patients mostly stay on the same medication regimen that led to the remitted state with only small changes in dosage, mostly to optimize tolerability. Once recovery is achieved, maintenance therapy starts, with the primary goal of prevention of recurrences. Clearly, the indication of maintenance therapy has to be reviewed for each single patient based on individual factors.

With respect to the above-described concepts relative to outcomes in major depression and corresponding therapeutic phases, it is obvious that two variables are crucial for long-term outcome:

- The threshold and definition of remission.
- Determining when recovery has set in, ie, the 6-month cutoff period.

Threshold and definition of remission
There is still no consensus regarding the best way of determining when the remitted state has been reached. As explained above, the HAMD rating scale, now in use for almost 50 years, has been widely used to assess symptomatic severity, response, and remission in clinical trials. Despite recent criticism, it remains the “gold standard” in academic and regulatory clinical trials. Other depression rating scales include the MADRS with its hypothesized better sensitivity to change, or the Inventory of Depressive Symptomatology (IDS), which reflect more contemporary definitions of depression, and are also used to define remission.

The most widely used criterion for remission is a HAMD-17 score of ≤7, which corresponds to a HAMD-7 score of ≤3. The recommendation of the ACNP Task Force is to use a score of ≤7 or even ≤5 on the HAMD-17 scale as criterion for remission. For the MADRS, scale cutoff scores of ≤8 or ≤9, <10, ≤10, ≤11, were suggested. However, there is recent evidence to support the use of more stringent scores on both the HAMD and MADRS scales. Patients with HAMD-17 scores ≤2 (or MADRS scores ≤4) show better psychosocial functioning than those with scores of 3 to 7 (or MADRS scores of 5 to 9). On the other hand, a problem with the use of very stringent definitions of remission is that healthy, nondepressed individuals may be labeled depressed. A literature review of control groups in clinical depression trials reported a mean HAMD-17 score of 3.2±3.2 (SD) among healthy control individuals. As already noted above, Michael Thase was able to separate depressed subjects from healthy controls and thus validate the HAMD-17 threshold of below 7 (Figure 2). In addition, in an analysis by our own group, a Hamilton-17 score ≤7 best corresponded to a Clinical Global Impression (CGI) score of 1 (corresponding to “normal, not ill”) in a large sample of naturally treated inpatients with MDE. However, Nierenberg very recently demonstrated for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study sample that the number of residual symptom domains was significantly associated with relapse even in patients meet-
ing criteria for full remission (Figure 3). This is of high clinical relevance as recent clinical studies indicate that 21% to 35% of patients in remission from an MDE had residual symptoms.24,25 In a recent analysis by our own group on 1014 naturally treated inpatients with MDE, patients meeting symptomatic criteria for full remission still showed an identical symptom pattern to that of patients meeting criteria for response, only at a much lower degree of severity.26

Both analyses indicate that residual symptoms in remitted patients resemble still-present illness activity more than anything else (eg, personality traits) and that the definitions we use are still in need of improvement. Two major options are currently under discussion. The first is to expand symptomatic remission criteria to areas of psychosocial functioning. The second option would be to also add a short time criterion for “sustained remission” as proposed by the ACNP Task Force (eg, 3 consecutive weeks). Clearly, a combination of both would probably be the most stringent and accurate method for defining remission. How long the time period of remission should last in order to declare a patient recovered will be reviewed in the next paragraph.

**Why has the cutoff for recovery been set at 6 months?**

- **Approach based on estimation of the duration of an MDE**

The crucial question is: what is the mean duration of an MDE? So far there are only few long-term observational studies available. Based on data from a 10-year follow-up study, Solomon et al calculated an average duration of depressive episodes of 20 weeks, with a median duration of 5 consecutive episodes of 22, 20, 21, 19, and 19 weeks.27 Similarly, Angst et al reported a median length of depressive episodes of 5.4 months in a 5-year follow-up of hospitalized patients with major depressive disorder.28

The sampling method used in these studies has been much criticized, and the recruitment of more chronic and more severe patient samples in such clinical follow-up studies has been dubbed “clinician’s illusion” or “Neyman bias.”29,30 Many individuals do not experience recurrences, and only those who do end up in clinical trials and thus represent the more chronic and severe cases. In other words, hospital-based clinical samples tend to be mostly “prevalence samples,” whereas epidemiological prospective follow-ups of patients with a first episode tend to be mostly “incidence samples.” This is why the natural history of major depressive disorder is usually best studied in prospective follow-up studies of individuals from their first lifetime episode onward, such as the NEmMH SeNVtah Enhcvehlth Survey and Incidence Study (NE-MESIS) and the Baltimore Epidemiologic Catchment Area (ECA) Follow-up Study.

The NEMESIS study followed a sample of 273 individuals with first lifetime major depressive episode over a period of more than 2 years. The approximated duration of depressive
episodes was 3 months. The methodologically most elaborate trial was the ECA, reported on by Eaton et al in 2008.30
Starting with a probability sample of 3481 household residents in 1981, 92 patients with a first lifetime episode of major depression were followed-up for at least 13 years. In this study, the median length of the depressive episode was also 3 months. Of note, about 50% of first-episode patients did not experience a second episode during follow up.

An important finding of this study was that there seemed to be a relationship between the total number of experienced episodes and the median episode duration. The first episode had a median duration of 20 weeks, patients with 3 or more episodes also had a median episode duration of 20 weeks, patients with 4 or more episodes had a median duration of 24 weeks, patients with 5 or more episodes had a median episode duration of 12 weeks, and patients with 9 or more episodes had a median duration of 6 weeks. Interestingly, once the total number of episodes was adjusted, there was neither a strong nor even a significant tendency for episodes earlier in the course to be shorter or longer than the episode occurring later in the course. In summary, this signals a pre-existing heterogeneity among patients with major depressive disorder with respect to the duration of episodes.30

- **Approach based on discontinuation trials**

Beyond the abovementioned descriptive pragmatic definition of recovery based on estimations of median episode duration, is an approach that is based on discontinuation trials. The theoretical backbone here is the assumption that once a patient has recovered, the underlying biological illness activity has abated and hence treatment can be safely discontinued. Probably one of the best prospective studies to address this issue and estimate the duration of MDEs in the absence of continuation treatment.33 Among patients who were remitters at maintenance baseline, 69% of those taking venlafaxine and 55% of those taking placebo were still remitters after 1 year.34 Certainly it has to be kept in mind that the patient sample suffered from recurrent depression with a mean current episode duration of 6 to 7 months, thus representing a more chronic study population.35 Nevertheless, this study gives fresh evidence for the efficacy of antidepressants during continuation over 6 months and during maintenance.

- **Limitations and pitfalls of these two approaches**

Using discontinuation data to estimate the duration of time in remission for a patient to be declared as recovered has 3 important pitfalls:

- Despite having achieved recovery after a period of 6 months in remission, patients can still experience a new MDE immediately thereafter.
- Achievement of recovery after 6 months does not necessarily exclude still-present biological illness activity of the affective disorder.
- Our knowledge of specific antidepressant action is still limited. So far we cannot distinguish whether symptoms are only “suppressed” by the medication or whether the MDE has returned.

However, to sum up, most data suggest a median duration of depressive episodes varying between 12 and 20 months. But since it can nowadays be assumed that at least a substantial proportion of depressive episodes are under treatment, we currently have no clear idea of how long episodes would last without treatment. Posternak et al have tried to address this issue and estimate the duration of MDEs in the absence of any somatic treatment.35 Out of 318 patients enrolled in the collaborative depression study, 130 patients experienced a recurrence over a 15-year follow-up period that initially went untreated for at least 4 weeks. Of those, 46 subjects received treatment, whereas the other 84 remained entirely untreated. In this study, recovery was defined as time to the first of 8 consecutive weeks with no or minimal symptoms. The total sample consisting of the 130 patients had a
median time to recovery of 23 weeks. But surprisingly the subgroup of untreated patients had a much shorter median time to recovery of 13 weeks.\textsuperscript{11} This example nicely illustrates the methodological difficulties in that research area. As the authors correctly state, the major reason for the shorter time period to recovery in the untreated sample is most probably the general difference between a treatment-seeking and a nontreatment-seeking depressed patient sample.\textsuperscript{32} As this was a nonrandomized trial, the results rather support prior studies showing that nontreatment-seeking patients have an inherently better prognosis than treatment-seeking patients.\textsuperscript{32} One possible methodological approach could be to meta-analyze placebo arms of controlled antidepressant trials in order to estimate the median time of a depressive episode in a treatment-seeking patient sample.

So far, we must assume, at least in case of treatment-seeking patients, that the depressive episode without treatment would last longer as discussed in the above-cited trials. In addition, since we have only one prospective study regarding the optimum length of continuation treatment, the 6-month duration still seems defensible. It could also well turn out that recovery should only be ascribed after 1 year, as suggested by Reimherr et al.\textsuperscript{33} With that definition it might also take longer to reach recovery. Reimherr et al showed that the mean time to recovery (defined as a 1-year period free of any episode) was 2 or 3 years for both men and women. However, periods of 4 months as suggested by the ACNP task force seem to be far too short.\textsuperscript{3} The main argument used here were reports that demonstrate that the highest chance for any relapse is within the first 4 months. But considering a wider range of trials on relapse rates, the highest risk indeed seems to be in the first or even 2 years after acute treatment.\textsuperscript{27,30}

Summary
To conclude, we should constantly remember the high heterogeneity of the disease major depressive disorder. With that in mind, an individualized approach is always preferable in good daily clinical practice. In this respect we should try to give the best estimate possible of each individual’s mean episode duration. Often patients remember earlier episodes, free of any treatment. With that information clinicians have a perfect estimate of how long continuation treatment should at least last in the individual patient. For research purposes and rougher guideline recommendations the 6-month threshold is still justifiable. Remission should still remain the main treatment goal in treating major depression. However, current criteria maybe need reconsideration, as residual symptoms, even in remitted patients, still seem to be associated with relapse.

References

Keywords: depression; relapse; recurrence; response; remission; recovery; continuation treatment; maintenance treatment; antidepressant

Pourquoi la limite rechute-récidive a-t-elle été fixée à 6 mois dans la dépression ?

Classer un épisode dépressif d’apparition récente en tant que rechute ou récidive présente des implications thérapeutiques importantes. Jadis on utilisait, dans les études sur les traitements antidépresseurs, des mesures très variées aux définitions arbitraires. Afin d’harmoniser et de standardiser ces définitions, la fondation MacArthur a mis en place un groupe spécial. Cet article résume les définitions actuellement utilisées pour la réponse, la rémission, la rechute, la récidive, la poursuite et le traitement d’entretien. Il s’interroge sur le bien-fondé de la définition de la rechute comme conséquence d’une rémission incomplète. Les deux critères les plus importants pour distinguer la rechute de la récidive sont le seuil de rémission et le temps passé en rémission avant que la guérison du patient soit reconnue. Pour la rémission, un seuil inférieur à 7 à l’échelle HAM-D17 items (Hamilton Depression Rating Scale), et pour la guérison, une durée de 6 mois en rémission, semblent maintenant acceptés par la communauté scientifique. Les études récentes sur les seuils de rémission, ainsi que le rôle des symptômes résiduels non reconnus dans le développement des troubles dépressifs sont passés en revue. Deux approches différentes basées sur la longueur de l’épisode dépressif et les données des études concernant l’arrêt du traitement antidépresseur expliquent et justifient la période de « 6 mois » permettant de déterminer la fin d’un épisode. Nous examinerons pour conclure les limites et les embûches liées à ces deux méthodes.
Clinical severity, treatment resistance, and recurrence of depression

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Severe depression is the most challenging subgroup of depression to treat; it is associated with greater suffering, increased disability, and increased morbidity and mortality. Treatment studies have found that some antidepressants are significantly more effective in treating severe depression than other, more conventional, antidepressants. Significant advantages are reported with escitalopram and with agomelatine both in individual studies and in meta-analyses of the data that define these antidepressants as superior. The issue of poor compliance with treatment in depression highlights the need for antidepressants that are not just superior in efficacy, but also superior in tolerability. Severe depression appears to be more prone to relapse and recurrence, and this finding emphasizes the need to prioritize the use of superior treatments in the long-term treatment of depression. The finding that severity of depression is one of the predictors of the development of resistant depression supports the view that severe depression should be aggressively treated with appropriate superior antidepressants to avoid the consequences of the depression becoming resistant.

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of the importance of establishing the severity of depression in order to identify the risk of disability, the risk of relapse, and the risk of the high levels of morbidity of the disorder. Severe depression is associated with increased mortality, higher morbidity, and greater disability than moderate or mild depression; it is also the group where the relapse rate in responders or remitters is highest. The treatment of severe depression is therefore one of the most challenging areas encountered by the physician. The assessment of severity also turns out to be a major tool in quantifying the proportion of individuals who respond well and achieve a reduction in symptom score to a low level in line with that when well. The concept of remission and the importance of remission as a target for treatment have been confirmed in recent studies.

Specific investigations of treatment and outcome in subgroups of patients with differing severity levels indicate that severe depression lies on a continuum of severity from mild and moderate depression with no obvious cutoff separating moderate from severe depression; rather there appears to be an increasing dimensional risk of disability with increasing severity of depression from moderate to severe illness. There is, however, no evidence to suggest that severe depression is a separate disorder although available treatments have been shown to have increased efficacy in the severe subgroup.

Definitions of severe depression
Severe depression is comparatively easy to recognize. Reasonable concordance between assessors can be achieved as to whether depression is mild, moderate, or severe, although this may be affected by the inherent variability due to differing levels of experience of the assessors. Quite marked cultural differences in assessment occur and these may be exacerbated by insensitive translation of global rating scales. A well-known example is the mismatch in meaning between the English word “moderate” and the French word “modéré,” which has led to difficulties in merging the data from studies carried out in different cultures when poorly translated global scales have been used.

Precise ratings of the severity of the individual symptoms of depression have helped to derive more easily defended definitions of severe depression identified by a score on an accepted depression rating scale. Currently, the most widely used criteria to define severe depression are a score of 30 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS), or a score of 25 or more on the 17-item Hamilton Depression Rating Scale (HAMD-17), which are the two most widely used pivotal scales. These definitions used in clinical treatment studies have the advantage that they appear to be in accord with clinical judgment. Other definitions have been used, for example, hospitalization or suicidal risk, but they are less specific and vary widely in different treating settings. Other factors unrelated to severity can play a role, for example the availability of hospital beds varies widely from country to country and even within a country from one region to another. Similarly, the risk of suicide is not necessarily an accurate marker of the severity of depression since suicidality is substantially altered by personality factors, by concomitant drug or alcohol abuse, by concomitant physical illness, by religious conviction, and by family support. The concept of melancholia, used in some countries to indicate severity, has been found to represent a loosely defined diagnostic subgroup of depression with varying levels of severity. Although melancholia as currently defined appears more common in severe depression, it can be found also in those with mild depression, moderate depression, and severe depression, and therefore the use of this term to define severity is inappropriate.

Differential efficacy in severe depression
Recognition of the importance of severe depression, in terms of associated increased morbidity, disability, and increased mortality, has stimulated research into the possible differential efficacy of various antidepressants. Initially, the analyses carried out found that selective serotonin reuptake inhibitors (SSRIs) were effective in both moderate and severe depression with no obvious difference in efficacy between the two groups. For example, in an elegant analysis of the placebo controlled data with citalopram the treatment effect, that is, the difference in response between citalopram and placebo, was constant in moderate and severe depression and there was no signal of any change in efficacy with increasing severity. In contrast, the treatment effect increased with increasing baseline severity with escitalopram and with agomelatine. The greatest response to placebo is observed in mild depression and the least in severe depression. Indeed, in mild depression the placebo response is so high that it is very difficult in clinical studies to identify a significant treatment effect of antidepressants. In the large placebo-controlled efficacy study of fluoxetine given in doses of 20, 40, or 60 mg in mild depression, defined by a baseline score of less than 20 on the HAMD, there was no perceptible difference between placebo and any dose of fluoxetine. It is probable that any pharmacological effect in these mildly depressed patients was marginal and the close attention and concern to be expected in the conduct of a clinical treatment trial had the consequence of improving all groups during the short duration of the study and obscured any difference. Factors such as the careful assessment and rating of depression in the context of a clinical study carry a nonspecific benefit that appears to be more marked in mild depression and less in severe depression.

Some antidepressants that are effective in moderate-to-severe depression have, however, been shown to have increased efficacy in the severely depressed subgroup. Analyses of the escitalopram clinical trial data were carried out to examine the possible influence of severity at the start of treatment on patients’ outcomes. When patients were categorized into cohorts of severity, a clear increase in efficacy was observed.
with increasing severity. \textsuperscript{2,10} If some, but not all, antidepressants are associated with this important feature of extra response in severe depression it is of great interest for the clinician to clarify in direct comparisons whether a significant difference between antidepressants can be established. The most scientifically rigorous way to investigate potential differences between antidepressants is to conduct individual studies with random double-blind assignment to treatment to reduce the risk of bias in the population studied. Providing that the studies are carried out under conditions of fair comparison, the results can show whether there are differences in efficacy and whether there is clear-cut superiority for some antidepressants.

A number of antidepressants have been compared and significant differences reported. Escitalopram was found to be more effective than citalopram in treating severe depression defined as a baseline MADRS score of 30 or more\textsuperscript{11,12} and also more effective than paroxetine.\textsuperscript{13} More recently, agomelatine was found to show increasing treatment effect (difference from placebo) with increasing severity of baseline depression in an analysis of the pivotal placebo-controlled studies.\textsuperscript{8} The greater treatment effect observed in the more severe patients suggested that agomelatine might also have advantages compared with other antidepressants in treating more severe depression. This has been confirmed on the pivotal efficacy measure in a prospective randomized double-blind study in severe depression comparing agomelatine with fluoxetine.

The severity of depression in this study was defined as having a baseline score 25 or more on the HAMD 17-item scale, and agomelatine was shown to be significantly superior to fluoxetine. Previous studies in moderate and severe depression have shown the superiority of agomelatine in comparison with sertraline\textsuperscript{14} and venlafaxine.\textsuperscript{15} Venlafaxine has itself a reputation of being more effective in severe depression\textsuperscript{16} though the evidence from formal studies is sparse. A large meta-analysis reported a modest, but significant, increase in the percentage of remissions (6%) with increasing baseline severity.\textsuperscript{17} This finding is supported by the superiority of venlafaxine demonstrated in a double-blind randomized comparison with fluoxetine in a largely severe depression population.\textsuperscript{18} Extra efficacy in severe depression is now regarded by many as the hallmark of the superior antidepressant.

The results from comparisons of individual antidepressants are supported by a retrospective meta-analysis of several studies, though in this analysis the agomelatine studies were excluded.\textsuperscript{19} The use of meta-analyses has its drawbacks since they are almost always conducted post hoc and they generally make the assumption that every study is equally fair, valid, and useful. Attempts to exclude biased or unfair comparison studies such as when the dose of one antidepressant can be raised to a maximum while the other remains low\textsuperscript{20} or when the population is already resistant to one of the treatments\textsuperscript{21} are rare. Nevertheless, despite their weaknesses, meta-analyses can provide support for the findings from individual comparisons that antidepressants differ in efficacy and tolerability. Identifying the antidepressants that have superior efficacy is an important step in guiding treatment choice. We need to concentrate our treatment efforts, giving priority to the use of antidepressants that are superior, and also, since compliance with treatment is such a problem in depression, to those that additionally have a better tolerability profile close to that seen with placebo.

**Discontinuation symptoms**

Abrupt termination of antidepressant treatment is in almost all cases associated with the appearance of discontinuation symptoms.\textsuperscript{22} Discontinuation symptoms have been reported with all classes of antidepressants since the early studies with imipramine. In some cases, it appears that these discontinuation symptoms may destabilize the clinical status and induce relapses. The discontinuation symptoms, which usually appear in the first few days after stopping treatment and reach maximal severity in the first week, may well be mistaken for relapses. This phenomenon complicates the design of the relapse prevention studies, which require that responders or remitters to the treatment under investigation, for example an antidepressant, are then randomized to receive treatment with either the same antidepressant or placebo under double-blind randomized conditions.

Some antidepressants appear to be more prone to produce discontinuation symptoms than others, eg, paroxetine\textsuperscript{23} or venlafaxine.\textsuperscript{24} Some antidepressants have a lower propensity to cause discontinuation symptoms, eg, fluoxetine\textsuperscript{24} or escitalopram,\textsuperscript{25} but only agomelatine has been found to be completely free of discontinuation symptoms. The clear difference between antidepressants in the rate of associated discontinuation symptoms is illustrated by a placebo-controlled discontinuation study that investigated rates in agomelatine and paroxetine. Stopping agomelatine treatment was associated with no signal of discontinuation symptoms compared with continuing agomelatine. In contrast, in the same study, after stopping paroxetine, given in a low dose of 20 mg, up to 45% of patients showed discontinuation symptoms.\textsuperscript{26}

**Discontinuation symptoms and relapse**

The need for long-term treatment of depression to prevent relapse following response to treatment and to reduce the risk of recurrence has long been established and is universally recommended. Improving long-term outcome is of particular concern for those who suffer severe depression, given the potential serious consequences. The clinically significant efficacy of antidepressants in long-term treatment is supported by an overwhelming weight of evidence in the literature. One example is the long-term placebo-controlled study of agomelatine, carried out largely in severe depression, which found that agomelatine has a powerful ability to reduce the risk of subsequent relapses or recurrences. This ability is reflected in
the strikingly low number of patients needed to treat (NNT) in order to show a significant advantage compared with placebo.27 There is also some indication in the agomelatine database that the risk of relapse is low in the mild depression sub-group suggesting that mild depression may not be the target for long-term antidepressant treatment. In placebo-controlled studies mild depression has a high spontaneous response rate, and evidence to support the need for long-term treatment would therefore be difficult to obtain. Mild depression might be a lower priority for both short- and long-term treatment.

We can have less confidence in the evidence of efficacy in relapse prevention derived from studies where the abruptly discontinued treatment is associated with frequent or trouble-some discontinuation symptoms. For example, in the relapse prevention study of fluvoxamine there was a high and rapid relapse rate, which was associated with high levels of discontinuation symptoms.28 To overcome the problem it is now routine procedure in a secondary analysis to exclude from the analysis data from the first month after stopping treat-ment to try to discount the discontinuation symptoms. A relapse prevention study with agomelatine is perhaps the first where the results are uncontaminated by a possible increase in the relapse rate associated with discontinuation symptoms, since such symptoms are not a problem with agomelatine. The efficacy of agomelatine in relapse prevention is therefore more securely based than other antidepressants that are prone to discontinuation symptoms and were tested using the same design.

Resistant depression
Nonresponse to antidepressants is common and is reported in between 30% and 50% of patients treated with antide-pressants in randomized double-blind placebo-controlled clinical studies. Surprisingly few studies have investigated what happens to these patients and as a result the evidence base on which advice can be given is limited. The short duration of the acute studies, normally 6 to 8 weeks, leaves unanswered the question as to whether there may be a further response if treatment were contained longer. This could be the case, but the longer 12-week placebo-controlled studies, which also report similar high levels of nonresponse, suggest other-wise.

The treatment of resistant depression is a pressing clinical problem that dominates the practice of almost all special-ists. In the US, a range of treatments are licensed as adjuncts in resistant depression, but, in the EU, regulatory recognition of the problem is more limited. This stems partly from the complicated definition of resistant depression used by the EU,29 which requires both a prospective demonstration of res-i stance and demonstration that patients have not responded to two different antidepressants from different pharmacologi-cal classes, each given in an adequate dosage for sufficient duration. Moreover, a treatment proposed for resistant depres-sion has to show persistence of efficacy compared with place-bo for at least 6 months. The evidence supporting the valid-ity of these complicated requirements is trivial and appears to be based on a single meta-analysis, which included unfair comparisons, that showed a modest advantage in remis-sion, though not responders, using these criteria.30

Other much larger studies have failed to find this advan-tage.31,32 In a very large survey of resistant depression across Europe the Treatment Resistant Depression Group found that switching classes of antidepressants was not helpful and that continuing with the same antidepressant for longer was asso-ciated with a significantly better response. In a prospec-tive study in resistant depression, switching nonresponders from citalopram (a SSRI), to desipramine (a tricyclic norepi-nephrine reuptake inhibitor) was associated with significantly fewer responders than staying on the same medication. The problem with switching antidepressants comes partly from the discontinuation symptoms on stopping the previous antidepres-sant and partly from the slow onset of action of the new antidepressant, normally around 6 weeks. The effect of these findings should be to encourage prescribers to use an-tidepressants that have low or no discontinuation symptoms and also to use antidepressants with superior antidepressant efficacy including a faster onset of antidepressant action.

The criteria for defining treatment resistance have led to studies that have shown that the key criterion is the failure to respond to a single course of treatment with an approved dose for adequate duration.33,34 The extra requirement of demonstrat-ing a failure to respond to a second treatment adds little and delays the diagnosis. The suggestion that an antidepres-sant from a different class must be tried to establish treat-ment-resistant depression is patently inaccurate and merely delays the correct diagnosis even further.

The predictors of resistant depression are well known.35 Most of these factors relate to severity of depression and also include comorbidity with any anxiety disorder (which of course increases the severity), the presence of suicidality, which is frequently severity related, and failure to respond to treatment of the first episode of depression. This suggests that resistance to treatment is an enduring feature that persists from one episode of depression to the next and emphasizes the need to use the more effective, superior antidepressants early, before resistance becomes established.

The same finding provides a rationale for seeking a possible genetic basis for nonresponse and resistance. The finding that polymorphism of the short arm of the serotonin trans-porter increases vulnerability to stress and increases levels of nonresponse36 has been confirmed in a number of studies. It now appears from the studies of the Treatment-Resistant Depression Group and the STAR*D studies (Sequenced Treatment Alternatives to Relieve Depression) that a number
of other genetic factors such as COMT (catechol-O-methyltransferase) also are also associated with increased resistance.

The finding that severity of depression and associated features is a predictor of treatment-resistant depression is provocative, and this raises the uncomfortable question that initial treatment with weaker conventional antidepressants may in some way induce resistance. In this context, current guidelines that are influenced by economic considerations, such as those of the National Institute for Health and Clinical Excellence (NICE) committee, and suggest using the weakest treatments first and without discussion of the superior efficacy of some antidepressants, now appear unacceptable.

Severe depression is associated with increased morbidity and mortality as well as increased treatment resistance and should be prioritized for accurate diagnosis and special treatment. We need to rethink our treatment recommendations and treat severe depression aggressively to achieve response and remission with those antidepressants that have been shown to be particularly effective.

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References
La dépression sévère est le sous-groupe de dépression le plus difficile à traiter ; il est associé à une plus grande souffrance, à une augmentation de l’incapacité et de la morbidité et de la mortalité. Des études thérapeutiques ont trouvé que certains antidépresseurs étaient significativement plus efficaces dans le traitement de la dépression sévère que d’autres antidépresseurs plus classiques. L’escitalopram et l’agomélatine ont montré des avantages significatifs à la fois dans des études individuelles et dans des métaanalyses de données qui les définissent comme plus efficaces. Le problème de la mauvaise observance des traitements antidépresseurs souligne la nécessité de disposer de médicaments non seulement plus efficaces mais mieux tolérés. La dépression sévère semble plus exposée à la rechute et à la récidive, d’où le besoin d’utiliser en priorité des traitements plus efficaces à long terme dans la dépression. Le fait que la sévérité de la dépression soit l’un des prédicteurs du développement d’une dépression résistante est un argument en faveur d’un traitement agressif de la dépression sévère avec des antidépresseurs adéquats plus efficaces afin d’éviter les conséquences d’une dépression devenant résistante.

Keywords: depression; relapse; recurrence; morbidity; mortality; antidepressant; treatment compliance; treatment resistance; escitalopram; agomelatine
A network of complex relationships exists between stress, depressive mood or the spectrum of depressive disorder, and cardiovascular disease, in particular coronary heart disease. Depressive mood and major depressive episodes can both be considered as risk factors for the development of cardiovascular disease, even after controlling for behaviors at risk for cardiovascular disease. Recurrent depression, but not single major depressive episode, is associated with the development of atherosclerosis and arterial calcifications. Type A behavior pattern and, more recently, work stress and cynical hostility, were also examined as predictors of cardiovascular disease. Incident post–myocardial infarction depression predicts cardiac mortality and new onset of cardiac events. Coronary heart disease and depression share common genetic vulnerabilities (eg, serotonin transporter [5-HTT] polymorphism), which interact with environmental factors and medical triggers, such as acute coronary syndrome. The continuum between depressive episode and depressive disorder, applied to cardiovascular patients, and the respective times of onset of cardiac events and depressive symptomatology, must be taken into account in order to determine the appropriate time and type of mood disorder treatment.

Medicographia. 2011;33:138-144 (see French abstract on page 144)
Depressive mood, MDE, or recurrent depression as risk factors for cardiovascular disease

The possibility that depression has an impact on the development of coronary heart disease (CHD) or atherosclerotic lesions in initially healthy subjects has led to controversial findings. In 1987, Booth-Kewley and Friedman showed in a meta-analysis a strong association between depression and CHD, but most of the studies included in that review were cross-sectional.10 Actually, in the late 80s, very few studies used a prospective cohort design. This situation changed in the next decade, but most of the studies assessed depressive symptomatology using self-administered questionnaires, without any standardized interview for performing Diagnostic and Statistical Manual of Mental Disorders, 3rd or 4th Editions (DSM-III or DSM-IV) diagnoses of MDE or depressive disorder.

In a further meta-analysis based on 11 selected studies, clinical depression was assessed only in three of the studies, whereas in the remaining eight studies, depressive mood was measured alone.3 In this meta-analysis, pooling all the studies, overall relative risk (RR) for the development of CHD in depressed subjects was 1.64 (95% confidence interval [CI], 1.29-2.08), but clinical depression (RR, 2.69; 95% CI, 1.63-4.43) was a stronger predictor than depressive mood (RR, 1.49, 95% CI: 1.16-1.92). Among the studies using a clinical diagnosis of depression, the nationally representative Mini-Finnland Health Survey covered 8000 individuals and consisted of a 6.6-year follow-up: an increased risk of coronary death was found in clinically depressed persons, both with and without cardiovascular diseases at entry. The authors concluded that “the hypothesis that depression is a cause of cardiovascular diseases requires further study.”11

In a study based on a follow-up of a survey of psychiatric disorders in the general population—the Baltimore cohort of the Epidemiologic Catchment Area (ECA) Study—a history of MDE or dysphoria (2 weeks of sadness) was assessed in 1981 using the Diagnostic Interview Schedule (DIS), a widely used tool in psychiatric epidemiology, and self-reported myocardial infarction (MI) was assessed in 1994.15 The odds ratio (OR) for MI associated with a history of MDE was 4.54 (95% CI, 1.65-12.44), independent of coronary risk factors, whereas the OR for MI associated with a history of dysphoria was 2.07 (95% CI, 1.16-3.71). Moreover, the use of tricyclic antidepressants and benzodiazepines was not predictive of MI.

The Johns Hopkins Precursors Study was a prospective, observational study of 1190 male medical students who were enrolled between 1948 and 1964 and who continued to be followed up.13 During a median of 37 years follow-up, the incidence of clinical depression was measured by means of mailed surveys with direct questions concerning the occurrence of depression and associated treatment. Self-reports of depression were confirmed by a committee of physician reviewers who were unaware of the study hypothesis. The cumulative incidence of clinical depression was 12%. Subjects who developed clinical depression drank more coffee than those who did not, but did not differ in terms of cardiovascular risk factors (baseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity, or family history of coronary artery disease). Multivariate analysis showed that clinical depression was associated with greater risk for subsequent CHD (RR, 2.12; 95% CI, 1.24-3.63) or MI (RR, 2.12; 95% CI, 1.11-4.06), and was still an independent risk factor for CHD 10 years after the onset of depression (RR, 2.1; 95% CI, 1.1-4.0).

In another study, after controlling for known cardiovascular risk factors, a self-reported history of treatment for depression was also independently associated with subsequent MI in 5564 treated hypertensive patients without prior cardiovascular disease (hazard ratio [HR], 2.10; 95% CI: 1.04-4.23).14 None of these studies separately assessed the predictive value of single MDE vs recurrent MDE regarding the development of cardiovascular diseases. This was the purpose of a series of studies on female populations. In 336 healthy middle-aged women from 1 of the 7 sites of the Study of Women’s Health Around the Nation, a prospective study of the perimenopausal transition, carotid plaque was assessed using a B-mode ultrasonography and psychiatric diagnoses were assessed using the Structured Clinical Interview for the DSM-IV Axis I Disorders–Non-Patient Edition (SCID-IV). The risk of

**Selected abbreviations and acronyms**

<table>
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<th>Abbreviation</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>CES-D</td>
<td>Center for Epidemiological Studies Depression Scale</td>
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<td>CHD</td>
<td>coronary artery disease</td>
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<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
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<td>DepreMi</td>
<td>Depression after Myocardial Infarction [study]</td>
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<td>ECA</td>
<td>Epidemiologic Catchment Area [study]</td>
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<tr>
<td>ENRICHED</td>
<td>Enhancing Recovery in Coronary Heart Disease [trial]</td>
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<td>EPIC</td>
<td>European Prospective Investigation of Cancer [study]</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases–10</td>
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<tr>
<td>MDE</td>
<td>Major Depressive Disorder</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MIND-IT</td>
<td>Myocardial Infarction and Depression–Intervention Trial</td>
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<tr>
<td>SADHART</td>
<td>Sertraline AntiDepressant Heart Attack Randomized Trial</td>
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<td>SCID-IV</td>
<td>Structured Clinical Interview for the DSM-IV Axis I Disorders–Non-Patient Edition</td>
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<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Program</td>
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<td>STAR*D</td>
<td>Sequenced Treatment Alternatives to Relieve Depression</td>
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Depression: isolated episodes or lifetime disorder?

plaque was twofold in women with a lifetime history of recurrent MDE relative to women with no history of depression (OR, 2.30; 95% CI, 1.10-4.82), whereas lifetime history of a single MDE was not associated with plaque.\textsuperscript{19} Similar findings were published regarding coronary and aortic calcifications in 58 African-American and 152 white healthy middle-aged women.\textsuperscript{16} This association was in part mediated by the waist-to-hip ratio. A recent publication confirmed that among 149 middle-aged healthy women who reported no heart disease, stroke or diabetes at baseline, women with recurrent MDE (n=33) had greater progression of coronary artery calcification, assessed using computed tomography measures on two occasions, approximately 2¼ years apart, than did women with a single or no episodes.\textsuperscript{17}

Other publications examined the role of depression timing as a risk factor for cardiovascular events, even if depressive mood was assessed using only self-administered questionnaires. In a prospective cohort of 4493 elderly Americans followed for 6 years, free of cardiovascular disease at baseline and enrolled in the Cardiovascular Health Study, the Center for Epidemiological Studies Depression Scale (CES-D) score was annually computed.\textsuperscript{18} The cumulative CES-D mean at last visit before any cardiovascular event was associated with development of CHD and all-cause mortality, using time-dependent, proportional-hazards models. As expected, cumulative CES-D mean was higher in subjects with a history of depression at baseline and, interestingly, in women, but not in men with baseline hypertension or smoking.

In another prospective cohort study of 3701 men and women aged >70 years, CES-D depressive symptomatology was also measured on three occasions during a 6-year period to distinguish persons who were newly (depressed at baseline, but not at 3 and 6 years before baseline) and chronically depressed (depressed at baseline and at 3 or 6 years before baseline).\textsuperscript{19} Subjects were then followed for a median period of 4 years. Their risk of subsequent CVD events and all-cause mortality was compared with that of subjects who were never depressed during the 6-year period. In men, but not in women, newly depressed mood was associated with an increased risk of cardiovascular mortality, new cardiovascular events, and new CHD events, after adjustment for traditional confounding variables, suggesting more direct pathophysiologic mechanisms such as endothelial dysfunction, inflammation, increased blood clotting, and decreased fibrinolysis. In further studies, due to repeated negative findings, Type A as a cardiovascular risk factor was abandoned and replaced by a more specific component of type A, namely, hostility, and especially cognitive or cynical hostility.

Type A individuals are supposed to be focused on achievement by work and to actively seek out challenging situations. Two main models of work stress have been proposed. In a prospective cohort study with a mean follow up of 25.6 years on 812 employees free from any cardiovascular disease at baseline both Karasek’s and Siegrist’s models of work stress (respectively “job strain,” a combination of high demands at work and low job control, and “effort-reward imbalance”) predicted cardiovascular mortality: HR=2.2 (95% CI, 1.2-4.2) for high job strain and 2.4 (95% CI: 1.3-4.4) for effort-reward imbalance, after adjustment for age and sex. The association remained significant after additional adjustment for smoking, physical activity, systolic blood pressure, cholesterol concentration, and body mass index.\textsuperscript{25}

In the INTERHEART study (not an acronym), a case-control design on 11 119 patients with a first myocardial infarction compared with 13 648 age-matched and sex-matched controls, patients reported higher prevalence of stress at work and at home, financial stress, and major life events in the past year. The highest OR, adjusted for age, sex, geographic region and smoking, were found for permanent stress at work (OR, 2.14; 99% CI, 1.73-2.64) and permanent stress at home (OR, 2.12; 99% CI, 1.68-2.65).\textsuperscript{24}

Therefore, according to the studies, the role of depression as a risk factor for cardiovascular disease appears as a time-dependent or a dose-dependent effect.

**Stress and coronary heart disease**

Early in the 1980s, a stress-prone personality trait defined as Type A behavior pattern, characterized by hard driving, competitive behavior, and a potential for hostility, was found in several prospective studies as associated with an increased risk for fatal as well as nonfatal CHD.\textsuperscript{22} Stress may affect health-related behaviors such as smoking, diet, alcohol consumption, or physical activity, which in turn may influence the risk of coronary heart disease, but, generally, results are adjusted for these confounding variables, suggesting more direct pathophysiologic mechanisms such as endothelial dysfunction, inflammation, increased blood clotting, and decreased fibrinolysis. In further studies, due to repeated negative findings, Type A as a cardiovascular risk factor was abandoned and replaced by a more specific component of type A, namely, hostility, and especially cognitive or cynical hostility.

**Depressive episode/disorder and stress and cardiovascular risk factors – Consoli**

In another case-control study, 97 consecutive patients with a first episode of coronary heart disease, interviewed with Paykel’s Interview for Recent Life Events, reported significantly more life events, as well as more mood disorders than matched controls. The difference regarding life events was similar in patients with and without mood disorders and concerned all the categories of events, excepted “entrances” (introduction of new people, such as marriage), eg, “exits” (departure of a person from the social field of the subject, such as the death of a close family member), socially desirable (promotion) as well as undesirable (major financial problems) events, and controlled (initiation under subject’s control or choice) as well as uncontrolled events.25

**Prognostic value of depression following a coronary event, according to depression type**

About 1 in 5 acute coronary syndrome (ACS) patients meets criteria for MDE, and of these patients, 50% or more have had depression symptoms in the past. The prognostic value of depressive disorder, regarding cardiac outcome, in patients with already established CHD, is based on much more convergent findings than the role of depression as a cardiovascular risk factor in healthy individuals. As early as in late 1980s Carney et al showed in 52 patients undergoing cardiac catheterization and subsequently found to have significant CHD, that major depressive disorder was the best predictor of major cardiac events during the 12 months following catheterization. The predictive effect was independent of the severity of CHD, left ventricular ejection fraction, and smoking.26

In 1993, Frasure-Smith et al showed that major depression in 222 patients hospitalized following a MI was as an independent risk factor for mortality at 6 months (adjusted HR, 4.29; 95% CI, 3.14-5.44).27 In 1995, the same research team published its results relating to an extended follow-up period of 18 months, showing that both the Diagnostic Interview Schedule (DIS) diagnosis of MDE (OR, 3.64; 95% CI, 1.32-10.05) and elevated Beck Depression Inventory (BDI) scores (OR, 7.82; 95% CI, 2.42-25.26) were significantly related to 18-month cardiac mortality.28 Adjusting for clinical confounding variables did not change the results, but contrary to BDI, MDE was no still predictive of cardiovascular deaths in patients who survived to 6 months. Multivariate analyses showed that anxiety and history of major depression each had an impact independent of each other, as well as of measures of cardiac disease severity.29

Many further studies replicated these first findings.30 The question remains whether the association between depression and mortality in patients with ACS is confounded by incomplete adjustment for measures of known prognostic markers. In a prospective survey on 457 ACS subjects, neither depression measure (MDE assessed using a standardized interview or BDI score) was associated with the Global Registry of Acute Coronary Events (GRACE) risk score, the most comprehensive empirically derived index of clinical mortality predictors. MDE and depressive symptom severity each predicted mortality after controlling for GRACE score and left ventricular dysfunction (HR [adjusted for MDE], 2.51; 95% CI, 1.45-4.37).31 No significant differences were found in GRACE scores between participants with initial MDE, as compared with those with recurrent MDE.

A growing literature has recently been dedicated to the differential prognostic value of incident vs ongoing and recurrent depression in patients with ACS. De Jonge et al assessed a total of 468 MI patients for the presence of an International Classification of Diseases–10 (ICD-10) depressive disorder within the year after index MI. During the 2.5-year mean follow-up period, compared with nondepressed patients, those with incident depression had an increased risk of cardiovascular events (adjusted HR, 1.76; 95% CI, 1.06 to 2.93), but not those with nonincident depression (adjusted HR, 1.39; 95% CI, 0.74 to 2.61).32 New-onset depression—but not isolated pre-MI depression—was also related to cardiac death in an 8-year follow up in 588 post-MI subjects; in the subgroup of subjects with post-MI depression, pre-MI depression did not convey any additional risk of cardiac mortality.32 Using the BDI in 750 patients who had unstable angina pectoris and myocardial infarction, 23.2% of the participants self-reported a history of depressed mood for >2 years, and 31.3% had elevated BDI scores at index hospitalization, with 14.0% reporting persistent depressive symptomatology with an onset before the index hospitalization. History of depressed mood was found in 44.7% of subjects with elevated BDI compared with 13.4% in the rest of the population studied. After controlling for prognostic indicators, such as cardiac disease severity, medical history, and smoking, depressive symptomatology during hospitalization was significantly predictive of mortality, but depressive history was not.33

Similar findings were published by Parker et al,34 who recently proposed a more sophisticated classification of depression in 489 patients experiencing an ACS and undergoing a standardized interview a few days following their admission, then 1 month later: the poorer cardiovascular prognosis was associated with “incident depression” (no depression at admission, but depressed at 1 month) and “recurrent depression” (history of depression prior to the admission, then new episode at 1 month assessment); the best with “no depression” (never depressed), “prior depression” and “noncontinuing depression” (depression at admission, whatever the history of depression, but no depression at 1 month); intermediate prognosis was associated with “continuing depression” (depression at admission and still depressed at 1 month).35

In the Depression after Myocardial Infarction (DepreMI) study, a naturalistic follow-up study of 475 patients admitted for MI, BDI scores during hospitalization and at 3, 6, and 12 months post-MI were analyzed, using latent class analysis. One out
of 5 classes was characterized by significant and increasing depressive symptoms (4.0%). Subjects in this class had a higher risk for a new cardiovascular event compared with subjects without depressive symptoms.36

Controlled trials focused on psychosocial distress, and especially depressive mood in patients hospitalized for an ACS were rather disappointing, regarding cardiac outcomes. SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial) was a double-blind, placebo controlled, randomized trial comparing the safety and antidepressant efficacy of sertraline vs placebo in 369 patients with ACS who met criteria for MDE. In this trial, baseline MDE severity and failure of MDE to improve substantially during treatment with either sertraline or placebo were strongly and independently associated with long-term mortality.37 Fifty-three percent of MDEs began before hospitalization for the index episode of ACS: they responded more frequently to sertraline than to placebo (63% vs 46%, respectively; OR, 2.0; 95% CI, 1.13-3.55) whereas depression with onset beginning after hospitalization showed a high placebo response rate (69% vs 60%, respectively).38 Multivariate analysis indicated that onset of the current episode before the index episode of ACS, history of MDE, and baseline severity independently predicted the sertraline-placebo response ratio.

In the multicenter randomized Myocardial INfarction and Depression–Intervention Trial (MIND-IT) on the effects of antidepressant treatment for post-MI depression, patients were enrolled in double-blind, placebo-controlled treatment with mirtazapine and, in the case of insufficient treatment response after 8 weeks, open treatment with citalopram. The 18-month event rate (cardiac mortality or cardiac-related hospital admission) was 25.6% among nonresponders, 11.2% among untreated control subjects, and 7.4% among responders.39 Gender differences were also noted in Linden’s meta-analysis on 23 trials comparing a psychological treatment to a control group on a total of 9856 coronary patients: the mortality benefits appeared only in men, even after controlling for age differences.40 Moreover, trials initiating treatment at least 2 months after a cardiac event showed greater mortality benefits than those initiating treatment right after the event.

Finally, a poorer cardiac outcome in patients presenting with CHD and a comorbid depressive disorder could also be explained by a suboptimal access to standard therapeutic procedures, as demonstrated by the publication of Druss et al. Compared with CHD patients with no mental disorder, the use of revascularization procedures in patients presenting with affective disorders was significantly lower (RR=0.51 for percutaneous transluminal coronary angioplasty, and RR=0.63 for coronary artery bypass graft surgery).41 The likelihood of undergoing catheterization (RR=0.65) was also lower, but among patients who underwent catheterization the reduction in the use of revascularization procedures was no longer significant (RR=0.75 for percutaneous transluminal coronary angioplasty, and RR=0.94 for coronary artery bypass graft surgery, respectively). Thus, access to and content of medical care, eg, catheterization in patients with CHD symptoms, may plausibly be influenced by depression history.

**Common genetic factors for CVD, depression, and depression responsiveness to antidepressants**

The association between cardiovascular disease, especially CHD, and depressive disorder, cannot be totally explained by reciprocal causal effects; common genetic factors to both vulnerabilities are also involved.

In twin studies, both depression and CHD appear heritable. In the only twin study to consider depression and CHD jointly, the correlation across heritabilities was 0.42, suggesting that nearly 20% of variability in depressive symptoms and CHD was attributable to common genetic factors.42 Genetic variation related to inflammation has been primarily examined in relation to CHD, whereas genetic variation of the serotonin system has been primarily examined in relation to depression, although both pathways are involved in CHD and depression. The S (short) allele of the serotonin transporter (5-HTT) gene was shown to reduce transcription of this gene and thus reduce serotonin reuptake. A gene-environment interaction was suggested, individuals with one or two copies of the S allele exhibiting more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the L (long) allele.43 In 2509 genotyped patients with MI, depressive symptoms were more common in patients with the S allele. Cardiac post-MI events were also more frequent in patients with the S allele than in those without it, and the increased risk for cardiac events became insignificant after an adjustment for depressive symptoms, indicating a possible mediating role of post-MI depression.44 CHD outpatients carrying an S allele have a higher mean score for perceived stress than L/L homozygotes45; genetic vulnerability to depression could thus interact with a physical stressing situation such a CHD condition.

**Stress and cardiovascular condition as risk factors for depressive recurrence**

Several characteristics have been described as contributing to depressive recurrence: age at onset/number of episodes, severity, psychiatric comorbidity, family history, internal attributes, neuroticism, poor social support, and stressful life events.46 Comorbid somatic condition has been less examined as a risk factor for depressive recurrence.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study carried out in 1500 patients, subjects with recurrent depression were older, had an earlier age of onset, and were more likely to have a positive family history of depression than first-episode patients. Their mean score on the Cumulative Illness Rating Scale (CIRS)—a 14-item interview
that gauges the severity/morbidity of general medical conditions relevant to different organ systems—was also higher, even though this difference was largely attributable to patients with 10 or more episodes, who reported the greatest number of comorbid medical illnesses.47

In the late 80s, Schleifer et al had already noted that depression following myocardial infarction was not associated with the severity of cardiac illness, but with the presence of non-cardiac medical illnesses.48

In the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial (2481 depressed or socially isolated patients with MI), the adjusted ORs for having an MDE increased linearly with medical comorbidity, as measured by a modified version of the Charlson Comorbidity Index. This relationship remained after adjusting for CHD severity. The relationship between severity of depression and medical comorbidity was also maintained after excluding somatic symptoms of depression.49

In 88 patients suffering from an ACS, a clinical interview was performed to assess current and past diagnosis of MDE. CHD severity was assessed in all patients by coronary angiography. Neither in-hospital MDE status nor history of depression were significant predictors of CHD severity, but the interaction term between both was (higher CHD severity in patients without any history of depression and with incident depression). Follow-up analyses showed that patients with first-time, incident MDE had significantly more severe CHD compared with patients with recurrent MDE.50 Authors suggest that ACS patients without a history of depression have normal vulnerability to depression, but because their CHD is more severe than those patients with past episodes of depression, they experience a first-time reactive depression in response to the significant physiologic and psychological stress. In these patients, incident MDE can be triggered by underlying cardiac disease. Another tentative explanation is that ACS patients with incident depression appear to have more advanced coronary vascular disease and that these patients may be more vulnerable to a certain type of depression termed vascular depression. Recurrent depression in ACS patients more likely resembles depression seen in the general population. Common risk factors for depression in the general population such as lower educational level and higher neuroticism are also seen in nonincident post-MI depressed patients. For individuals with recurrent depression severity is not a trigger for MDE: they may experience an exacerbation of a previously existing vulnerability, which is triggered by the ACS. Time course of depression in CHD patients can thus be understood as a result of genetic vulnerability, history of mood disorders, personality, severity of CHD, and comorbid somatic factors. Such complexity likely accounts for specific difficulties in treating depression in cardiovascular patients, in addition to symptom overlap and all the other obstacles related to a condition that is associated with multiple diagnoses.

References

Quel est le rôle du stress et des facteurs de risque cardio-vasculaire dans le continuum entre épisode dépressif et trouble dépressif ?

Il existe un ensemble de relations complexes entre le stress, l’humeur dépressive ou le spectre des troubles dépressifs, et les maladies cardio-vasculaires, en particulier l’insuffisance coronaire. L’existence d’une humeur dépressive et la survenue d’épisodes dépressifs majeurs peuvent, tous deux, être considérés comme des facteurs de risque contribuant au développement des maladies cardio-vasculaires, même après ajustement sur les divers comportements à risque cardio-vasculaire. La dépression reconnectée, contrairement à la survenue d’un épisode dépressif majeur isolé, est associée au développement de l’athérosclérose et de calcifications arterielles. Le profil comportemental de type A, et plus récemment, le stress au travail et l’hostilité dite « cynique » (c’est à dire surtout la composante cognitive de l’hostilité), ont aussi été étudiés comme facteurs prédicatifs de pathologies cardio-vasculaires. C’est en fait la dépression incidente post-infarctus qui prédit la mortalité cardiaque et la survenue de nouveaux événements cardio-vasculaires. La maladie coronaire et la dépression partagent des vulnérabilités génétiques communes (par ex. le polymorphisme du transporteur de la sérotonine [5-HTT]), qui interagissent avec des facteurs environnementaux et des événements précipitants liés à la santé, tels qu’un syndrome coronaire aigu. La notion d’un continuum entre épisode dépressif et trouble dépressif, appliqué aux patients atteints de maladies cardio-vasculaires, ainsi que la chronologie respective de survenue des événements cardiaques et de la symptomatologie dépressif, méritent d’être pris en compte pour déterminer le meilleur moment et type de traitement du trouble de l’humeur.
Depression is the most frequent presentation of bipolar disorder. Several studies have reported that the long-term course of the illness is dominated by depressive rather than manic symptoms, with a direct negative impact on patient functioning. Despite its high morbidity and mortality, it is a field of research that has been neglected until recent years. A high percentage of bipolar patients are initially misdiagnosed as having unipolar depressive disorder. This mistake carries significant negative consequences for the treatment of this population and for outcomes. Therefore, it is essential to establish an accurate distinction between bipolar and unipolar depression in order to make an accurate and early diagnosis, leading to improvements in treatment and course of illness. This could also help clarify whether bipolar depression and major depressive disorder are separate diagnostic entities or belong to the same illness spectrum. This review aims to analyze the differences between unipolar and bipolar depression and identify possible predictors that may influence the “conversion” from unipolar depression to bipolar disorder. New proposals and future challenges in this area will also be discussed.

**Course and outcome patterns of depression: from unipolar episode to bipolar disorder**

by M. Reinares and E. Vieta, Spain

Bipolar disorder is a high prevalent, chronic, recurrent illness with devastating consequences when untreated because of high rates of morbidity and mortality. About 15% of severe bipolar patients die by suicide and the percentage of patients who attempt suicide more than once is even higher. These attempts mostly occur during depressive phases. The long-term course of the illness is dominated by depressive rather than manic symptoms. Recent studies suggest that depression has a direct and negative impact on functioning and these deficits appear to persist even during remission. Furthermore, subsyndromal symptoms can not only impair psychosocial functioning, but can also lead to a recurrence. In spite of the deleterious consequences of bipolar depression, it has been a neglected field of research for a long time. All the risks mentioned could be lowered by means of an early diagnosis and prophylactic treatment.

To be able to distinguish between bipolar and unipolar depression is crucial, as the treatment of both conditions differs considerably. This distinction is necessary in order to ensure accurate and early diagnosis, and to improve the pharmacological treatment of depression and understand the biology involved in each condition. It would reduce the economic burden and improve the health and quality of life of these patients.
patients. It also could help clarify whether bipolar depression and major depressive disorder are separate diagnostic entities or whether they belong to the same illness spectrum as different manifestations of the same underlying disorder.

**Diagnostic issues**

Unipolar and bipolar depression were first described by Leonhard and this distinction was validated by Angst, Perris, and Winokur and coworkers who showed that clinical, familial, and course features supported the nosological differentiation between both forms. Officially recognized in 1980 by DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition), this subtyping of unipolar/bipolar was further established in DSM-IV (4th Edition) and DSM-IV-R (4th Edition, Text Revision), both of which distinguish between bipolar type I and type II. Although major depressive disorder is classified separately from bipolar disorder, the criteria for unipolar and bipolar depression are identical, and emphasis is placed upon the euphoric condition and not upon differences in the depressive episodes. However, the impact of antidepressant treatment is different, clear for unipolar patients, unclear and sometimes self-defeating for bipolar patients, increasing the risks of (hypo)manic switch or rapid cycling. Due to misdiagnosis, many bipolar patients are less likely to receive mood stabilizer medications. Furthermore, some of the illness treatments might be less effective when they are introduced in patients who have had many previous episodes and the impact of a late introduction of mood stabilizers on top of antidepressants may carry high switch rates and increased suicidality.

It has been reported that about 7.5 years elapse from the first time the patients ask for medical help and the time an accurate diagnosis of bipolar disorder is made. A survey of bipolar patients involved with National Depressive and Manic-Depressive Association support groups pointed out that 69% of patients were initially misdiagnosed, on average four psychiatrists were consulted before an accurate diagnosis was made, and unipolar depression was the most frequent misdiagnosis. As suggested by Goodwin and Jamison, there are five primary causes for misdiagnosis: (i) patients’ lack of insight with regard to manic as opposed to depressive symptoms; (ii) clinicians’ neglect of information available from family members or other third parties; (iii) clinicians’ relative focus on euphoric rather than dysphoric or irritable mood as a criterion for hypomania; (iv) the structure of DSM-IV, which by separating bipolar from all depressive disorders has obscured the close relationship between early-onset recurrent depression and bipolar disorder; and (v) widespread interest in and use of “second-generation” antidepressants.

It is difficult to establish a correct differential diagnosis based on cross-sectional information, without obtaining data about the patient’s course of illness. By definition, (hypo)mania plays an essential role in the understanding of the bipolar condition of a mood disorder. Sometimes, especially when dealing with a bipolar disorder type II, diagnosis can be difficult when hypomanic episodes are not clearly detected. Furthermore, some subjects have a hyperthymic or cyclothymic temperament with mood disturbances that can sometimes be seen as borderline personality traits. Hence, the bipolar nature of a depressive episode could be difficult to establish. In fact, it has been pointed out that depressive polarity was strongly associated with a higher number of years undiagnosed. A recent study found that the delay to first treatment was associated with being depressed for longer, greater severity of depression, greater number of episodes, more days of ultradean cycling, and fewer days euthymic. Another confusion factor to take into account is comorbidity with other psychiatric disorders. The high prevalence of comorbidities in bipolar patients has a negative impact on prognosis and sometimes also makes an accurate diagnosis more difficult to establish. The most frequent misdiagnosis includes substance-use disorders, anxiety disorders, personality disorders, and attention deficit hyperactivity disorder. To sum up, bipolar depression, which is often related to comorbidity, disability and mortality, is still largely unknown and frequently underestimated, which may engender a more severe course of the illness.

**Clinical features of unipolar and bipolar depression**

Several authors have tried to define the clinical specificity of bipolar depression. Unfortunately, some studies do not consider the distinction between bipolar subtypes. Although there are no pathognomonic characteristics specific to bipolar depression compared with unipolar depressive disorder, when both conditions have been analyzed, some clinical and epidemiological differences can be described (Table I).

The age of onset of the first depressive episode in bipolar disorder has been found to be earlier than that observed in unipolar depression. Regarding the course of the illness, it has been reported that bipolar depressed subjects are more likely to report more prior episodes and shorter episode duration. Other typical characteristics of bipolar depression are lability of mood and hypomanic symptoms during depression. Goldberg et al found that two thirds of the subjects with bipolar depressed episodes had concomitant manic symptoms, most often distractibility, flight of ideas or racing thoughts, and psychomotor agitation. They observed that manic symptoms during depression demarcated a more severe and psychopathologically complex clinical state. It has also been reported that the stronger the manic component, the higher the mean values for novelty seeking and reward de-

<table>
<thead>
<tr>
<th>SELECTED ABBREVIATIONS AND ACRONYMS</th>
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<tr>
<td>HCL-32 Hypomania Checklist</td>
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<tr>
<td>MDQ Mood Depression Questionnaire</td>
</tr>
<tr>
<td>SAD-P Screening Assessment of Depression-Polarity</td>
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Depression: isolated episodes or lifetime disorder?

Depression: from unipolar episode to bipolar disorder – Reinares and Vieta

Predictors of bipolar outcome in depression

The percentage of patients initially identified with “unipolar” depression who experience manic episodes varies widely across studies, but may be as high as 50%. To identify those unipolar patients who, in the long-term, “become” bipolar patients is another way of obtaining more information about bipolar depression. When the predictors are analyzed, they are quite similar to those aspects described in cross-sectional comparative studies between unipolar and bipolar depression. In a retrospective study published in 1976, Dunner and colleagues found that up to 21% of type I and type II bipolar patients had previously been hospitalized due to “unipolar depression.” Akiskal et al proposed eight criteria predictive of the “bipolarization” of a depression, and suggested calling “pseudounipolar depression” the episodes that will show its bipolarity afterwards. They found the following predictors: treatment-induced hypomania, family history of bipolar disorder, strong inheritability, depression with hypomania and mania, continuous multigenerational familial transmission, postpartum onset and early onset (before age 25). Long-term studies have shown that those patients who became bipolar were more likely to show psychosis at the index depressive episode. Younger age at onset, chronicity of the index episode, and family history of mania have also been reported.

Table I. Differences between bipolar and unipolar depression.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bipolar depression</th>
<th>Unipolar depression</th>
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</thead>
<tbody>
<tr>
<td>Onset and characteristics of episodes</td>
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<td></td>
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<tr>
<td>Early age of onset</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Number of prior episodes</td>
<td>Higher</td>
<td>Lower</td>
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<tr>
<td>Duration of episodes</td>
<td>Shorter</td>
<td>Longer</td>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Postpartum episodes</td>
<td>More frequent</td>
<td>Less frequent</td>
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<tr>
<td>Substance abuse</td>
<td>More frequent</td>
<td>Less frequent</td>
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<tr>
<td>Psychotic symptoms</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Atypical symptoms</td>
<td>More frequent</td>
<td>Less frequent</td>
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<tr>
<td>Lability of mood</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Hypersomnia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Manic symptoms during depression</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Appetite loss/weight loss</td>
<td>Less frequent</td>
<td>More frequent</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of bipolar disorder</td>
<td>More frequent</td>
<td>Less frequent</td>
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<tr>
<td>Manic switch with antidepressants</td>
<td>More frequent</td>
<td>Less frequent</td>
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In an 11-year follow-up study composed of 559 subjects with a major depressive episode, Akiskal and coworkers found that up to 12.5% later developed a manic or hypomanic episode, which confirms its inclusion in the so-called “bipolar spectrum.” Twenty-two patients (3.9%) had a full-blown manic episode, becoming bipolar type I, and 48 (8.6%) had at least one episode of hypomania, confirming its status as belonging to the bipolar II disorder. Except for greater acuteness, severity, and psychotic symptomatology, bipolar I converters were similar to major depressive disorder nonconverters. In contrast, bipolar II converters were robustly distinguished from those with major depressive disorder who remained unipolar on the basis of self-report measures of mood lability, energy/activity, and daydreaming. This profile was associated with early age at onset of major depressive disorder and pleomorphic psychopathology beyond the usual affective realm, high rates of substance abuse, as well as educational, marital, and occupational disruption and minor antisocial acts prior to discrete hypomanic episodes. Bipolar II switchers had a more protracted and tempestuous course with shorter well intervals. Overall, descriptions of temperamental instability during major depressive disorder episodes provided useful clinical information for predicting which depressed patients will switch to bipolar II.

Recently, a 5-year prospective study showed that 2.8% and 8.9% of unipolar major depressive patients switched to bipolar I and II disorder, respectively. Together with severity, predictors for diagnostic switch included psychiatric comorbidity such as obsessive-compulsive disorder, social phobias, and symptoms of cluster B personality disorders.

A great number of individuals with the so-called soft or subsyndromal states belong to the bipolar spectrum by virtue of their positive family histories, their pharmacological response,
and their tendency to progress to full clinical disorder. Based on a sample of patients with bipolar II disorder and major depressive disorder, Benazzi and Akiskal aimed to identify validated bipolar markers. Lower age at onset (before 21 years), higher major depressive episode recurrence, mixed depression, and bipolar family history were significantly more common in bipolar II disorder. Early onset was the most discriminative feature of this major depressive disorder subgroup at possible higher risk of shifting to bipolar disorder. The authors suggested that early age at onset of depression represents a marker of a genetically based recurrent or polyphasic mood disorder.

New proposals

Based on the fact that some clinical characteristics are more common in both bipolar depression and major depressive disorder, respectively, or are observed in unipolar depressed patients who “convert” to bipolar disorder over time, Mitchell et al have suggested a probabilistic approach. Instead of proposing a categorical diagnostic distinction between bipolar and unipolar depressive disorder, they recommend a likelihood approach as follows (see Table II).

This approach uses a set of sociodemographic and clinical variables to establish which patients with depression are more or less likely to have an underlying bipolar disorder, and it is based on differences between subjects with bipolar disorder and major depressive disorder other than the presence or absence of manic symptoms. Therefore, the assessment of the presence of (hypo)manic symptoms would be complemented by other aspects related to the clinical history to make an accurate diagnosis. Although this approach should be carried out with new data and be further explored, the use of probabilistic models has been reinforced when the criteria of actual classifications systems have been discussed.

As previously mentioned, Solomon et al suggested a preliminary screen for bipolar disorder in patients with a depressive episode by means of assessing the presence of delusions during the current episode of major depression, the number of prior episodes of major depression, and a family history of major depression or mania.

The influence of subsyndromal depression on psychosocial functioning and on future mood recurrences points to the need to introduce treatments with the aim of achieving full remission. Based on the fact that the risk of subsequent recurrence and impairment increases with each new episode and that there is a poorer response to treatment when it is implemented later in the course of the illness, recent proposals have been made regarding the application of clinical staging to bipolar disorder. The staging model suggests a progression from prodromal to more severe and refractory presentations. However, early intervention in bipolar disorders depends on the ability to identify individuals at high risk of developing the illness. Failure to identify minor elated states leads to misdiagnosis of bipolar spectrum patients as unipolar. It is essential to strive to make appropriate distinctions among various forms of depression and differentiate them diagnostically, prognostically, and therapeutically from ordinary unipolar major depressive disorder.

A GREATER LIKELIHOOD OF DIAGNOSIS OF BIPOLAR I DEPRESSION SHOULD BE CONSIDERED IF ≥5 OF THE FOLLOWING FEATURES ARE PRESENT

Symptomatology and mental state signs
- Hypersomnia and/or increased daytime napping
- Hyperphagia and/or increased weight
- Other “atypical” depressive symptoms such as “leaden paralysis”
- Psychomotor retardation
- Psychotic features and/or pathological guilt
- Lability of mood/manic symptoms

Course of illness
- Early onset of first depression (<25 years)
- Multiple prior episodes of depression (≥5 episodes)

Family history
- Positive family history of bipolar disorder

A GREATER LIKELIHOOD OF DIAGNOSIS OF UNIPOLAR DEPRESSION SHOULD BE CONSIDERED IF ≥4 OF THE FOLLOWING FEATURES ARE PRESENT

Symptomatology
- Initial insomnia/reduced sleep
- Appetite and/or weight loss
- Normal or increased activity levels
- Somatic complaints

Course of illness
- Later onset of first depression (>25 years)
- Long duration of current episode (>6 months)

Family history
- Negative family history of bipolar disorder

Table II. Likelihood of diagnosis of bipolar I depression and of unipolar depression.

A better knowledge of the characteristics that permit discrimination between unipolar and bipolar disorder, together with a good anamnesis complemented with information from family members and a higher use of screening tools, could facilitate an increase in the detection of bipolar disorder in patients with depression. The Mood Disorder Questionnaire (MDQ) may help to increase recognition of bipolar disorder.

A recent study showed that the MDQ yielded a positive screen rate of bipolar patients with a diagnosis of unipolar disorder and a current depressive episode. The Hypomania Checklist (HCL-32) can also help to identify the hypomanic component of depressive episodes and increase the detection of bipolar disorder.
tion rate of both bipolar disorder and minor bipolar disorders. Rating tools should be introduced systematically in primary care, paying special attention to young people.

A contentious issue is whether (hypo)mania that occurs during treatment of “unipolar” depression is, following DSM-IV, an antidepressant-induced mood disorder or, as suggested by some experts, the precipitation of an underlying bipolar disorder. A high increase in the number of patients who would be considered bipolar if the duration criteria of hypo(manic) symptoms were more flexible has also been reported.60 Therefore, major depressive disorder seems to be overdiagnosed at the expense of bipolar disorder. Using a broader concept and a more comprehensive screening of bipolarity, Zimmermann et al48 have suggested that major depressive disorder is a heterogeneous concept including a large group with subthreshold bipolar disorder. In contrast to the dichotomical models, the development of a validated bipolar spectrum concept has been introduced to assist in more differentiated research and provide a treatment model for affective disorders, which may help reduce the underrecognition of bipolarity.39 This model unifies categorical classification with a dimensional view, as some proposals for future diagnostic classification systems have suggested.60

Conclusions

Despite depression being the most frequent presentation of bipolar disorder associated with high morbidity and mortality, it has been a neglected field of research. Fortunately, in recent years, a number of studies have shed some light on this topic. There are areas of overlap between both forms of depression, although some differences have also been found. The distinction between bipolar and unipolar depression would assist in making an accurate and early diagnosis, in improving treatment, and in reaching a better understanding of each condition which, in turn, would contribute to improving illness outcome. The new editions of the forthcoming diagnostic classifications will face the challenge of improving the discriminant validity of bipolar and unipolar depressions. New treatments will also need to be tested in the two indications, hopefully providing a final answer to the unsolved question of the efficacy and safety of antidepressants in bipolar depression. Meanwhile, the best way to discriminate between unipolar and bipolar depression is the course and outcome of the condition. To what extent both disorders are merely different course patterns of one condition is still a matter of debate.

The authors of this study would like to thank the CIBERSAM, and appreciate the support of the Generalitat de Catalunya for the Bipolar Disorders Group (2009 SGR 1022).

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La dépression est la manifestation la plus fréquente du trouble bipolaire. D’après plusieurs études, la maladie est, sur le long terme, dominée par des symptômes plutôt dépressifs que maniaques, influant négativement sur l’activité du patient. Malgré sa morbidité et sa mortalité élevées, ce domaine de la recherche a été négligé jusqu’à peu. Un pourcentage élevé de patients bipolaires sont initialement diagnostiqués à tort comme ayant un trouble dépressif unipolaire. Cette erreur induit des conséquences négatives significatives pour le traitement de cette population et pour ses suites. Il est donc impératif d’établir une distinction précise entre dépression bipolaire et unipolaire afin de poser un diagnostic exact et précoce, aboutissant à une amélioration du traitement et du cours de la maladie. Ceci pourrait aussi aider à savoir si la dépression bipolaire et le trouble dépressif majeur sont des entités diagnostiques distinctes ou appartiennent au même spectre pathologique. Cet article a pour but d’analyser les différences entre dépression unipolaire et bipolaire et d’identifier les éventuels facteurs prédictifs pouvant influer sur la « conversion » d’une dépression unipolaire en trouble bipolaire. Nous aborderons également les nouvelles propositions et les futures défis concernant ce domaine.

Keywords: bipolar disorder; major depression; unipolar depressive disorder; switch; outcome; spectrum
The long-term course of unipolar major depressive disorder (MDD) is characterized by high rates of recurrence and prolonged symptomatic chronicity. The primary goals of continuation and maintenance treatment are to prevent a fast relapse into depression or new episode of depression (recurrence). Adverse prognostic indicators for recurrence include: high number of previous episodes; residual symptoms at remission; previous longer episodes and chronicity; more severe previous episodes; onset early in life; concurrent dysthymic disorder (“double depression”); concurrent substance abuse or anxiety disorders; and family history of MDD in first-degree relatives. Key elements of long-term treatment include: pharmacotherapy; psychoeducation; and adherence monitoring. Extending treatment for an additional 6 months (continuation therapy) can reduce the likelihood of relapse by about 70%, and extending treatment for another 12 months or longer (maintenance therapy) can reduce the risk of recurrence. Most patients receive antidepressants during the acute and continuation phase, and the best treatment recommendation to prevent relapse and recurrence of depression is to continue the antidepressant medication at the same dose during these treatment phases as well. Randomized placebo-controlled efficacy studies (RCTs, usually conducted 1 or 2 years after remission) indicate that all major classes of antidepressants are effective in preventing recurrence of depression with about a twofold higher relapse rate with placebo treatment. Evidence suggests that the “newer” antidepressants have superior long-term efficacy and better tolerability compared with traditional antidepressants, eg, the tricyclics. Although concerns about the generalizability of results from placebo RCTs can be raised, RCTs testing the efficacy of a new antidepressant in comparison with placebo remain the gold standard for proof of efficacy requested by the regulatory authorities. Effectiveness trials studying patients in the “true world” provide additional important information, but due to methodological reasons they cannot replace placebo-controlled RCTs.

Major depressive disorder: a highly recurrent disease

Major depressive disorder (MDD) presents typically as a recurrent disorder. 50% to 85% of the patients who suffer a depressive episode will have another episode of major depression.1 The likelihood of a recurrence increases with the number of previous depressive episodes and the severity of the current episode. Patients who have had three episodes of major depression have...
a 90% chance of having another. Among other risk factors for recurrence of MDD, prior history of multiple episodes of MDD, early age at onset, persistence of dysthymic symptoms after recovery from an episode of MDD, presence of an additional, non-mood psychiatric diagnosis, and presence of a chronic physical disorder have been identified. Factors that have been associated with increased severity of subsequent depressive episodes include a history or a prior episode complicated by serious suicide attempts, psychotic features, or severe functional impairment.

Keeping these facts in mind, it is apparent that the primary goals of long-term, maintenance (prophylactic) treatment are to prevent a new episode of depression (a recurrence) and development of chronicity. A recurrence is an episode that appears after a completely asymptomatic period (remission) has been achieved for a 6-month period. The consideration of the patient’s course of illness and treatment history is essential for the implementation of maintenance phase therapy. Even though no definite recommendation can be given as to when prophylactic therapy should be initiated, it is clearly indicated in situations associated with a high risk of recurrence (Table I). In addition to the risk factors shown in Table I, patient preference, severity of functional impairments, and side effects experienced during the continuation phase also play a role in determining whether or not maintenance treatment should be implemented.

### Key elements of relapse prevention

Key elements of relapse/recurrence prevention treatment of recurrent depressive disorders include: (i) psychoeducation; (ii) pharmacotherapy; and (iii) adherence monitoring. Adjunctive depression-targeted psychotherapy may also be included in the treatment plan. Because maintenance treatment requires compliance with medication, education, and a close therapeutic alliance with patients and their families/friends are essential. Education does not only reduce treatment attrition, but also leads to a better outcome. Strategies to prepare patients and their families for maintenance treatment include education on the typical course of the illness, treatment options, medication effects and side effects, use of (daily) self-report instruments to track mood and early warning signs of relapse or recurrence, long-term perspectives, and projected end of treatment. A relapse prevention program (a low intensity intervention including enhanced patient education, visits with a depression specialist, telephone calls, symptom monitoring) for depressed patients in primary care significantly improved antidepressant adherence and depressive symptoms outcome in a randomized controlled 12-month trial compared with usual primary care.

### Relapse prevention in depression with antidepressant medication

Pharmacotherapy is the most studied treatment modality in the long-term treatment of recurrent MDD. Among the therapeutic options available, antidepressant medications, and lithium have received the most study. The majority of controlled trials investigating these medications in maintenance treatment demonstrated efficacy for relapse prevention. Likely reasons why antidepressants may be preferred to lithium are that patients are usually treated with antidepressants during the acute/continuation phase and that patients usually prefer to use medication that does not require regular monitoring by blood tests. The final choice of pharmacological agent does depend on how individual patients respond to and tolerate treatment with antidepressants and lithium. Patients’ preference and their own or their family member’s experience with maintenance treatment are also helpful in the choice of the medication.

### Antidepressants for relapse prevention

Randomized placebo-controlled studies (usually 1 or 2 years after remission) of antidepressants for relapse prevention treat-
ment of depression indicate that literally all major available antidepressants are effective in preventing relapse of depression: tricyclic antidepressants (TCAs), eg, amitriptyline, imipramine, nortriptyline; irreversible monoamine oxidase inhibitors (MAOIs), eg, phenelzine; selective serotonin reuptake inhibitors (SSRIs), eg, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); selective serotonin and norepinephrine reuptake inhibitors (SNRIs), eg, duloxetine, venlafaxine; bupropion; and agomelatine have been tested with positive results by either indicating significant lower relapse rates (with placebo about twice as high as with active agents) or a longer time to relapse compared with placebo treatment. To give an example: in a most recent study, the cumulative relapse rate at 6 months for agomelatine-treated patients was 21.7% and for placebo-treated patients 46.6%. The calculated effect sizes (and the active treatment–placebo differences) in these studies appear to be even higher compared with acute treatment studies. Relapse rates are high in the first months after remission in particular and decline with time. From naturalistic follow-up studies, the rates of relapse following remission have been estimated at 20% to 24% by 2 months, 28% to 44% by 4 months, 27% to 50% by 6 months, and 37% to 54% by 12 months.

A meta-analysis of discontinuation randomized controlled trials (RCTs) in patients with MDD reported that 60% of patients on placebo relapsed in the year after randomization and 29% relapsed in months 12 to 36. For clinical decision making it is also useful to express the relative benefit of an active treatment over placebo using the “number needed to treat” (NNT). The NNT concept represents one component of the complex benefit/risk estimation of antidepressant treatments. It represents the minimal number of patients who have to be treated to reach a benefit in one patient. In relapse prevention treatment studies, the active treatment–placebo difference seems to be even higher compared with acute treatment studies of antidepressants: in a pooled analysis of 31 RCTs in 4410 patients, a rounded NNT of 5 (4.34) for the relapse prevention during the first 12 months after successful acute treatment has been calculated.

In the majority of these relapse prevention trials, however, only responders to the drug tested during the acute phase were included in the continuation/maintenance randomized, double-blind treatment phase. This design has been described as introducing a potentially significant selection bias that limits the generalizability of results. Strictly speaking, findings are only relevant to the population of patients who are responsive to study medication during the acute phase. To overcome this selection bias, continuation and maintenance medication should be assessed among patients achieving initial remission through other means and antidepressant medications besides the maintenance drug. The latter design, however, is more difficult to conduct for obvious reasons (and subsequently more expensive) and brings up the question why patients should be treated in the continuation/maintenance phase with a medication that they have not responded to in the acute phase.

**Efficacy and effectiveness of antidepressants**

**Antidepressant efficacy**

There is an ongoing debate as to whether randomized, placebo-controlled trials are the best and only way to test if a medication is effective in certain patient populations. There is one clear answer to that: to receive approval for a specific indication, regulatory authorities, eg, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) request RCTs testing the efficacy of a new antidepressant in comparison with placebo or in comparison with placebo and a standard (comparator) drug. The term “efficacy” is usually defined as the power of an antidepressant to produce antidepressant effects under “ideal” conditions. According to the British National Institute for Clinical Excellence (NICE) it is defined as “the extent to which a specific treatment or intervention, under ideally controlled conditions (eg, in a laboratory), has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care.” The mean differences of scores on any applied depression rating scale (typically the Hamilton Rating Scale for Depression [HAM-D] or the Montgomery Åsberg Depression Rating Scale [MADRS]) between active antidepressant drugs and placebo shown in pivotal RCTs are used for decision making by the regulatory authorities to determine whether new antidepressants may receive approval or not. Unfortunately, placebo effect plays a significant role in clinical trials of MDD. Recent meta-analyses showed that the mean responder rate in placebo-treated groups was 29.7% and that this rate had been growing over the past decades of drug development. The further consideration of other additional efficacy indicators such as response and remission rates and the number needed to treat (NNT) is useful.

The efficacy of antidepressant medication in the acute treatment of MDD in adults is well proven by a large number of RCTs. This has been investigated in many RCTs comparing active antidepressants with placebo treatment and with active comparators. Most publications are reporting responder and remitter rates together with end-point differences in depression rating scales such as different versions of the HAM-D or the MADRS scale using the “last observation carried forward” (LOCF) method, which follows all included patients. Usual responder rates vary between 32% and 70%, and HAM-D17 differences between active and placebo treatment after 6 to 8 weeks of treatment often reach only 3 to 4 absolute points, but represent mean reductions in comparison to the scores before treatment of about 50% to 60%.

**Antidepressant effectiveness**

In contrast, “effectiveness” of an antidepressant drug can be achieved during the use of the substance in typical clinical circumstances and in larger populations of patients in the real
world. In most studies, responder and remitter rates are higher in effectiveness studies compared with RCTs. Serious concerns about the generalizability of results from placebo RCTs have been raised in the literature. The standard exclusion criteria of most trials, which have become much more stringent over the past decade, do exclude a significant number of patients suffering from suicidality, comorbid axis I disorders, and medical illnesses. In the case of trials investigating the efficacy of antidepressants, patients with a history of treatment failures and long depressive index episodes are generally also excluded from participation. Furthermore, simply the use of placebo, randomization, and blinding procedures excludes many patients who refuse study participation because of these procedures that may in their view reduce the chances of improvement. Ghaemi has estimated that fewer than 10% of depressed patients qualify for, and agree to, participate in available RCTs of antidepressants. Subsequently, the assumption in the world of clinical trials is that the research conducted on these 10% is generalizable to the other remaining 90% of patients. Although unproven, it may well be that results of a placebo-controlled RCT would be different if a significant proportion of these 90% were included in the trial. Nevertheless, according to NICE and regulatory authorities such as the EMA, RCTs remain the most important method for establishing treatment efficacy and estimating the clinical effectiveness of antidepressants. Approval based on effectiveness studies only would introduce other biases (eg, by unblinded ratings, no placebo as a comparator drug), resulting in false results.

**Comparative efficacy of antidepressants**

A relatively small number of studies have directly compared different medications for maintenance treatment in recurrent unipolar depression. A meta-analysis of studies comparing lithium with other antidepressants showed no conclusive advantage for lithium in the prophylaxis of unipolar illness. In one relatively small randomized, placebo-controlled 2-year maintenance study, lithium (serum level 0.8 to 1.2 mmol/L) was superior to imipramine (100 to 150 mg/day); the combination of lithium and imipramine was not superior to lithium alone. Another, larger randomized, placebo-controlled 2-year study reported better maintenance effects for imipramine (the mean daily dosage at the start of the maintenance phase was 137 mg, range 75 to 150 mg/day) than lithium (the mean serum lithium level at the start of the maintenance phase was 0.66 mmol/L, range 0.43 to 1.05 mmol/L). In the latter study, the combination of imipramine and lithium did not provide any advantage over imipramine alone in preventing depressive recurrences.

However, in a later reanalysis of the data, the same authors concluded that the results of the latter study could be accounted for by alternative explanations that are a consequence of the study design. One randomized, prospective, open, 2.5-year trial comparing lithium (average serum lithium level 0.59 mmol/L) with amitriptyline (average dosage 98 mg/day) found significantly better prophylactic efficacy for lithium.

**The question of dosing and additional psychotherapy in relapse prevention**

The majority of patients with a moderate/severe depressive episode receive antidepressants during the acute and continuation phase, and the best treatment recommendation to prevent recurrence of depression is to continue the antidepressant medication that was effective during the acute and continuation phase of treatment at the same dose during the maintenance phase. In two studies, the group of patients who received only half of the acute-phase dose of imipramine or paroxetine rather than the full dose, showed a significantly higher recurrence rate. Of course, in case of intolerance or disturbing side effects, the dose needs adaptation (decrease) in the clinical setting.

In the largest and probably most influential study of the use of antidepressants in maintenance treatment, a randomized 3-year placebo-controlled trial, survival analysis showed full-dose imipramine (mean dose at randomization 215 mg/day) with or without Interpersonal Therapy (IPT; weekly for 12 weeks, then biweekly for 8 weeks, and then monthly) to be the best maintenance treatment, followed by IPT with or without placebo, and then placebo. In this study of highly recurrent unipolar depression, all patients enrolled in the 3-year study, had remitted on the combination of imipramine and IPT, and all had remained well for 4 months of continuation therapy prior to randomization. A subsequent additional 2-year placebo-controlled study of the patients who completed the 3-year study showed that imipramine (average dose of 200 mg/day) was significantly better than placebo in preventing recurrence.

**Side effect profile: relevance for long-term treatment**

Side effects and tolerability of medications are key considerations in maximizing adherence to treatment, and they should be as minimal as possible. Even mild-to-moderate side effects during maintenance treatment may lead to noncompliance with the consequence of symptom worsening and increased risk of recurrence. Using medications with a more favorable side effect profile than the TCAs may facilitate patient compliance with pharmacotherapy, as long as these agents are effective in the maintenance treatment of depression. A number of more recent studies suggest that the “newer” antidepressants have superior long-term efficacy and better tolerability compared with traditional TCAs and tetracyclines. A randomized, placebo-controlled 2-year study comparing the efficacy of mirtazapine with that of amitriptyline found that the time to relapse was significantly longer in the mirtazapine group. Similarly, a double-blind 1-year study reported significantly greater improvement in some of the out-
come measures in the venlafaxine group compared with imipramine.41 Ideally, the rate and severity of side effects of the antidepressant medication should be at the level of placebo as demonstrated for agomelatine23 and other “newer” antidepressants.

Maintenance treatment options

There is growing recognition that prophylactic treatment of depressive disorders may be inadequate in a substantial proportion of patients. The maintenance treatment of patients with recurrent depression who experience recurrences during prophylactic treatment with standard agents, eg, antidepressants and/or lithium, is one of the most challenging issues in the treatment of these disorders. However, little data from formal studies are available to guide physicians in the maintenance treatment of patients suffering from recurrences during standard prophylactic treatment.12 Combination therapy administering two or even three antidepressants, maybe combined with lithium (or in case of refractoriness or intolerance lamotrigine or valproate), are treatment options for the clinician although there are little controlled data to support such polypharmacy. Figure 1 gives an algorithm for treatment options during the maintenance treatment phase.

Duration and discontinuation of maintenance treatment

The optimal moment to discontinue a longer-term medication is difficult to predict. Current evidence suggests that maintenance treatment should be continued as long as the risk of recurrence persists. That risk is often difficult to assess in the individual patient, particularly after a long period (years) of absence of symptoms/recurrence. It appears that the likelihood of a recurrence increases with the number of previous depressive episodes. However, some authors have argued that there is a similar risk of recurrence whether medication is discontinued after months or years of pharmacotherapy.42 There is good evidence from a controlled 5-year study that patients who benefited the most from continued prophylaxis were those receiving active full-dose medication for at least 5 years.38 Thus, for some patients, maintenance treatment is required for very long periods (eg, a decade) and for others it is required indefinitely.43 Three years maintenance therapy is appropriate almost as a routine for recurrent patients, particularly where an episode prior to the present one has occurred in the last 5 years or where remission has been difficult to achieve. Maintenance for 5 years or indefinitely is recommended for those patients at greater risk, particularly where two or three attempts to withdraw medication have been followed by another episode within 1 year. Only with long-term antidepressant treatment can the risk of development of serious depressive illness with a high relapse and suicide rate be stopped or at least reduced.

Figure 1. Therapeutic options for maintenance treatment of major depressive disorder.
Abbreviations: CBZ, carbamazepine; LAM, lamotrigine; MT, maintenance treatment; VAL, valproate.
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Treatment of depressive episode and prevention of depressive disorder – Bauer

References

Keywords: depressive episode; depressive disorder; recurrence; relapse; antidepressant; prevention; tolerability
ÉPISODE DÉPRESSIF : LE TRAITEMENT ANTIDÉPRESSEUR PRÉVIENT-IL LE RISQUE DE TROUBLE DÉPRESSIF ?

L'évolution à long terme du trouble dépressif majeur (TDM) unipolaire est caractérisée par des taux élevés de récidive et une chronicité prolongée des symptômes. Les premiers objectifs du traitement de consolidation et d'entretien sont de prévenir une rechute rapide de la dépression ou un nouvel épisode dépressif (récidive). Les indicateurs de mauvais pronostic pour la récidive sont : de nombreux épisodes antérieurs ; des symptômes résiduels lors de la rémission ; des épisodes antérieurs et une chronicité plus longs ; des épisodes antérieurs plus sévères ; un début précoce dans la vie ; un trouble dysthymique simultané (« double dépression ») ; une toxicomanie ou des troubles anxieux concomitants ; des antécédents familiaux de TDM dans la parentèle de premier degré. Les éléments clés du traitement à long terme comprennent : la psychoéducation ; et la surveillance de l’observance. Prolonger le traitement pendant 6 mois supplémentaires (traitement de consolidation) peut diminuer la probabilité de rechute d'environ 70 % et le prolonger de 12 autres mois ou plus (traitement d'entretien) peut diminuer le risque de récidive. La plupart des patients reçoivent des antidépresseurs pendant les phases aiguë et de consolidation, la meilleure recommandation thérapeutique pour prévenir la récidive et la rechute dépressive étant de poursuivre le traitement antidépresseur à la même posologie pendant ces phases. Des essais d'efficacité randomisés contrôlés contre placebo (ECR : essais contrôlés randomisés, généralement conduits 1 à 2 ans après la rémission) montrent que toutes les classes majeures d’antidépresseurs sont efficaces dans la prévention de la récidive dépressive alors que le taux de rechute sous placebo est environ deux fois plus élevé. Il existe des arguments en faveur d'une meilleure efficacité à long terme et d'une meilleure tolérance des « nouveaux antidépresseurs » comparés aux antidépresseurs traditionnels comme les tricycliques. Bien que l’extrapolation à la population dépressive générale des résultats issus des ECR contre placebo puisse soulever des réserves, les ECR testant l’efficacité d’un nouvel antidépresseur contre placebo restent la méthode de référence pour prouver l’efficacité demandée par les autorités réglementaires. Les études d’efficacité portant sur des patients dans le « monde réel » donnent des informations supplémentaires importantes mais, pour des raisons méthodologiques, elles ne peuvent remplacer les ECR contre placebo.
Most guidelines also recommend that patients with three or more Major Depressive Episodes should be maintained on antidepressants for at least 1 year and up to lifetime, with duration of maintenance therapy depending upon risk factors for recurrence and patient preference. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, patients should continue antidepressants for at least 2 years if they are at risk of relapse.

"The definitions of relapse and recurrence of a major depressive episode (MDE) proposed by the MacArthur Foundation Task Force have been more or less universally accepted. Relapse implies the loss of either response or remission and may be operationalized as the return of sufficient symptoms to meet criteria for an MDE for at least 2 weeks or an increase in Hamilton Rating Scale for Depression (HRSD) scores above a predetermined threshold for a minimum duration (eg, HRSD ≥16 for 2 weeks or more). Recurrence implies the emergence of a new episode of depression some time after the risk period for relapse within an identified episode, although the distinction between relapse and recurrence is probably more theoretical than pragmatic. These definitions provide a basis for comparative studies to examine relapse prevention across different treatment modalities (eg, pharmacotherapy, electroconvulsive therapy, or cognitive therapy) or within one modality (eg, selective serotonin reuptake inhibitor (SSRI) vs serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants)."

There is strong evidence to support relapse prevention strategies in the intermediate and long-term management of patients with a history of recurrent Major Depressive Episodes. Most placebo-controlled relapse prevention trials have evaluated the benefits of different antidepressant therapies (tricyclic, selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, and agomelatine) over 6-month to 3-year durations. Evidence-based psychotherapy studies, mainly cognitive behavioral therapy (CBT), mindfulness-based cognitive therapy (MBCT), and interpersonal psychotherapy (IPT), with and without pharmacotherapy, have also been carried out. Although there are considerable variations in methodologies, meta-analyses and guidelines support maintenance treatments with both antidepressants and psychotherapies. In general, patients with risk factors for recurrent episodes of depression should remain at the same dose of antidepressant medication for at least 2 years. Patients require frequent monitoring with an emphasis on modifiable risk factors for relapse, including comorbid disorders and treatment adherence. Those who relapse despite adequate medication therapy may benefit from additional CBT or MBCT. Discontinuation of medications requires gradual tapering. It is important to address individual patient factors in the long-term management of Major Depressive Disorder.

Guidelines for relapse prevention in the treatment of major depressive disorder

by S. H. Kennedy and F. M. Placenza, Canada

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Guideline recommendations for relapse prevention

The evidence to support continuation and maintenance antidepressant therapies in the long-term management of MDD is among the most robust in the mood disorders literature. Among guidelines developed for the treatment of Major Depressive Disorder (MDD), those of the British Association for Psychopharmacology (BAP), the Canadian Network for Mood and Anxiety Treatments (CANMAT), the National Institute for Health and Clinical Excellence (NICE), the Texas Medication Algorithm Project (TMAP), and the World Federation of Societies of Biological Psychiatry (WFSBP) are among the most current.10

There is a consensus that maintenance treatment should continue for a minimum of 6 months after achieving symptomatic remission and that the medication dose that was effective during acute treatment should not be reduced. Maintenance treatment for 6 to 9 months is acceptable for patients with one or two episodes who do not have additional risk factors for relapse.5 The presence of risk factors in patients who have had two episodes supports an extended period of maintenance therapy.5 These risk factors are summarized in the CANMAT guidelines (Table I).6 While the WFSBP guidelines concur with the general recommendations to maintain antidepressants at the same dose as the acute phase, these guidelines offer more support for lithium in preventing recurrence of unipolar depressive illness. They also emphasize the benefits of lithium prophylaxis in reducing the risk of suicide.9

Most guidelines also recommend that patients with three or more MDEs should be maintained on antidepressants for at least 1 year and up to lifetime, with duration of maintenance therapy depending upon risk factors for recurrence and patient preference.6 According to the NICE guidelines, patients should continue antidepressants for at least 2 years if they are at risk of relapse.7 Recommendations from the BAP guidelines are that, for patients with more than five lifetime episodes and/or two episodes in the last few years, medication should be continued for at least 2 years.8

Maintenance treatment beyond 2 years should be considered when factors such as older age, comorbid conditions, and other risk factors are present.7 There is also agreement that when the decision is made to discontinue an antidepressant, it should be done gradually to avoid discontinuation emergent symptoms. High-risk patients should be monitored regularly for early signs of recurrence after discontinuation of antidepressants. According to the CANMAT guidelines, evidence to support maintenance therapy for longer than 2 years has a less established evidence base, but certain risk factors, including earlier onset of depression, continuing psychosocial adversity, older age, and comorbid medical or psychiatric conditions, are indicators for extended maintenance treatment.6 In the NICE guidelines, patients who have relapsed despite adequate antidepressant maintenance treatment are considered candidates for combined medication and psychological interventions, particularly cognitive behavioral therapy (CBT) or mindfulness-based cognitive therapy (MBCT). MBCT is also recommended for people who are currently well, but have experienced three or more prior episodes of depression.7 Similar conclusions are reached in the BAP guidelines, which suggest the addition of CBT to medication for patients with residual symptoms or those with additional risk factors for relapse. The same group also concludes that interpersonal therapy (IPT) is not recommended as a sole maintenance treatment, although it may be a useful adjunct to antidepressants in patients with recurrent depression.5 Psychotherapy is not recommended as a sole treatment to prevent recurrence in the

Table I. Risk factors supporting long-term (2 years to lifetime) antidepressant maintenance.

<table>
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<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td>● Older age</td>
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<td>● Recurrent episodes (3 or more)</td>
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<tr>
<td>● Chronic episodes</td>
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<tr>
<td>● Severe episodes</td>
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<tr>
<td>● Psychotic episodes</td>
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<tr>
<td>● Difficult-to-treat episodes</td>
</tr>
<tr>
<td>● Significant comorbidity (psychiatric or medical)</td>
</tr>
<tr>
<td>● Residual symptoms (lack of remission) during current episode</td>
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<td>● History of recurrence during discontinuation of antidepressants</td>
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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>BAP</td>
<td>British Association for Psychopharmacology</td>
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<tr>
<td>CANMAT</td>
<td>Canadian Network for Mood and Anxiety Treatments</td>
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<tr>
<td>CBT</td>
<td>cognitive behavioral therapy</td>
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<tr>
<td>CORE</td>
<td>Consortium for Research in ECT</td>
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<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
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<tr>
<td>HRSD</td>
<td>Hamilton Rating Scale for Depression</td>
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<tr>
<td>IPT</td>
<td>interpersonal psychotherapy</td>
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<tr>
<td>MADRS</td>
<td>Montgomery-Åsberg Depression Rating Scale</td>
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<tr>
<td>MBCT</td>
<td>mindfulness-based cognitive therapy</td>
</tr>
<tr>
<td>MDE</td>
<td>Major Depressive Episode</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>PREVENT</td>
<td>Prevention of Recurrent Episodes of depression with VENlafaxine for Two years</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>TMAP</td>
<td>Texas Medication Algorithm Project</td>
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<tr>
<td>WFSBP</td>
<td>World Federation of Societies of Biological Psychiatry</td>
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Evidence to support relapse prevention strategies in major depressive disorder

Pharmacotherapy studies

Support for these guidelines on relapse prevention has steadily emerged over several decades. In a landmark relapse prevention trial, the Pittsburgh group evaluated the benefits of a tricyclic antidepressant (TCA) or IPT alone or in various combinations. Results of the survival analysis demonstrated a robust effect for imipramine at an average dose of 200 mg daily and a modest effect for IPT. The mean survival time for both imipramine-treated groups was approximately 2.5 years compared to 1.5 years for IPT and just under 1 year for the placebo control group. In the final phase of this project, 20 subjects who had remained in recovery up to 3 years were randomized to continue on imipramine (n=11) or to receive placebo (n=9) for a further 2 years. At the end of 5 years, 5 out of 9 receiving placebo had a recurrence of depressive episodes with a mean survival time of 54 weeks, while only 1 out of 11 receiving imipramine had a recurrence and the mean survival time was 99 weeks.

One of the first relapse prevention trials with a second-generation antidepressant compared responders to paroxetine who remained on the active treatment for 1 year to those who switched to placebo. There was a significantly lower rate of relapse and longer survival time in the paroxetine group. This was followed by a large systematic review of relapse prevention in which Geddes and colleagues (2003) identified 31 randomized trials (published or unpublished up to August 2000) involving patients who had responded to an antidepressant during acute treatment and were randomized to continue on the drug or switch to placebo. Although this analysis included trials out to 36 months, more than 58% lasted 6 or 12 months and the majority (81%) involved TCAs or SSRIs. The authors concluded that continuing treatment with an antidepressant reduced the odds of relapse by 70%, with an average of 41% of patients receiving placebo and 18% on antidepressant experiencing a relapse. The relative reduction in year 1 was 20%, corresponding to a number needed to treat of 5 patients.

Prevention of Recurrent Episodes of depression with VENlafaxine for Two years (PREVENT) was the first large trial to assess relapse prevention with an SNRI in patients with recurrent depression (defined as three or more prior episodes, two occurring within the past 5 years). The study employed a three-phase, double-blind, placebo-controlled methodology to examine two consecutive 1-year maintenance phases in which responders to venlafaxine ER were randomly assigned to remain on the medication or switch to placebo. At the end of each maintenance phase, patients receiving venlafaxine ER had a significantly longer time to recurrence and lower likelihood of recurrence compared with those who were switched to placebo (Year 1: 23% vs 42%; Year 2: 8% vs 45%).

In a subsequent meta-analysis involving SSRIs, SNRIs, and other second-generation antidepressants, Hansen and colleagues (2008) evaluated 23 placebo-controlled and 4 comparative trials. There were no differences in relapse and recurrence rates in the 4 head-to-head comparative trials. Among the placebo-controlled trials, the duration of randomized follow-up in 12 studies was less than 1 year, and 1 year or longer in the remaining 11 trials. The number of patients needed to treat to prevent 1 additional relapse was 5. In a recent update on the long-term treatment of depression with SSRIs and newer antidepressants, Reid and Barbui (2010) reaffirmed the benefit of continuing antidepressant treatment for at least 12 months following the treatment of an acute episode.

Agomelatine is a new antidepressant with a novel mode of action that has also been evaluated under relapse prevention conditions. Like the trials previously reviewed, agomelatine demonstrated similar efficacy in relapse prevention with a cumulative relapse rate of 21.7% for agomelatine compared with 46.6% for placebo over 24 weeks of maintenance therapy.

Psychotherapy studies

In parallel with the pharmacotherapy evidence for relapse prevention, a number of studies have demonstrated the benefits of evidence-based psychotherapies, particularly CBT and MBCT. While there is some support for IPT as a maintenance therapy, the evidence is less robust. For example, Schramm and colleagues (2007) reported a short-term (3-month) advantage for IPT over clinical management for relapse prevention in hospitalized depressed patients with MDD. However, this difference was not maintained at 1 year. Frank and colleagues (2007) also evaluated the potential preventative role of IPT at different frequencies in a large sample of women with recurrent unipolar depression who achieved remission with either IPT alone or in combination with an SSRI. Once-monthly IPT proved to be a good method of prophylaxis for the subgroup of women who achieved remission with IPT alone, but was less helpful in the group who required SSRIs in the initial phase of treatment. A summary of recommendations for evidence-based psychotherapies in maintenance treatment from the CANMAT guidelines are shown in Table II.

Despite the impressive evidence from these various controlled trials, adherence to relapse prevention strategies in natural practice trials is considerably less impressive. The investigators monitored, but did not control, the use of antidepressants during a 2-year follow up of remitted patients who had a history of recurrent depression and were candidates for maintenance antidepressant therapy. Only 42% maintained...
continuous antidepressant treatment, 38% received antidepressants intermittently, and 20% were without maintenance antidepressant therapy throughout the trial. Overall, based on a standardized minimum effective dose criterion, only 26% of patients received an antidepressant at or above the recommended guideline doses. In this study, there was no difference in rates of relapse between intermittent and continuous antidepressant groups, but those patients who received additional preventive cognitive therapy had the lowest relapse rates.25

In a subsequent report involving the same cohort of patients, Bockting and colleagues (2009) compared relapse rates after 5.5 years in “treatment as usual” (TAU) versus TAU augmented with a course of modified cognitive therapy. While the overall relapse rate was high (79%), there was a significantly lower rate in the augmented group (75%) compared with the TAU group (95%).26

Neurostimulation studies
Among the neurostimulation therapies, only electroconvulsive therapy (ECT) has an adequate evidence base to provide guidelines for its use in relapse prevention.27 The main clinical dilemma following successful treatment of an acute depressive episode with ECT is the selection of optimal maintenance therapy. In general, antidepressant treatments that failed primary episode with ECT is the selection of optimal maintenance therapy during the first 6 months.28 However, results from two large collaborative studies, the Consortium for Research in ECT (CORE)29 and the Columbia University Consortium,30 support a combination of nortriptyline and lithium for relapse prevention. In the CORE study, maintenance ECT was as effective as the combination therapy during the first 6 months.28 However, there is insufficient evidence to recommend an optimal frequency for maintenance ECT and only modest evidence to support continuation of ECT in the long term.30

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RECOMMANDATIONS POUR LA PRÉVENTION DES RECHUTES
DANS LE TRAITEMENT DES TROUBLES DÉPRESSIFS MAJEURS

Il existe de solides arguments en faveur de l’instauration de stratégies de prévention des rechutes dans la prise en charge à moyen et à long terme des patients ayant des antécédents d’épisodes dépressifs majeurs. La plupart des études contrôlées contre placebo portant sur la prévention des rechutes ont évalué les bénéfices des différents traitements antidépresseurs (tricycliques, inhibiteurs sélectifs de la recapture de la sérotonine, inhibiteurs de la recapture de la sérotonine et de la noradrénaline, agomélatine) sur des durées allant de 6 mois à 3 ans. Des études basées sur les preuves, portant sur les méthodes psychothérapeutiques, ont également été conduites, avec et sans traitement médicamenteux, principalement des études de thérapie cognitivo-comportementale (TCC), de thérapie cognitive basée sur la pleine conscience (TCPC) et de psychothérapie interpersonnelle (PIP). Malgré d’importantes variations dans la méthodologie, les métaanalyses et les recommandations préconisent des traitements d’entretien incluant à la fois des antidépresseurs et des méthodes psychothérapeutiques. En général, les patients ayant des facteurs de risque de récidive d’épisodes dépressifs devraient rester à la même posologie d’antidépresseurs pendant au moins 2 ans. La surveillance de ces patients doit être étroite, et insister sur les facteurs de risque de rechute modifiables, qu’il s’agisse de comorbidités ou de l’observance du traitement. Les patients chez qui survient une rechute malgré un traitement médicamenteux approprié pourraient bénéficier de l’ajout d’une TCC ou TCPC. L’arrêt des médicaments doit être progressif. Il est important de prendre en compte les facteurs individuels du patient dans la prise en charge à long terme du trouble dépressif majeur.

Keywords: serotonin reuptake inhibitor; serotonin and norepinephrine reuptake inhibitor; agomelatine; cognitive behavioral therapy; electroconvulsive therapy

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Keywords: serotonin reuptake inhibitor; serotonin and norepinephrine reuptake inhibitor; agomelatine; cognitive behavioral therapy; electroconvulsive therapy
Major depressive disorder (MDD) is a mental disorder that frequently affects individuals of all ages. Patients may experience a single episode or recurrent ones. The impact the disease has on an individual’s everyday life is important, resulting in a substantial economic burden imposed on society, with the majority of the costs being generated outside the health care systems. Several cost-of-illness studies on major depression focus on the direct medical, and in some cases, direct nonmedical costs. Indirect costs are not frequently assessed even if they impose a significant burden on society, particularly during the acute phases of the disease. Pharmacological treatment is an important component of direct medical costs, estimated to account for 6% to 29% of total direct health care costs. Major depressive episodes represent an additional burden for society due to increased costs imposed on the health care system and higher productivity losses when compared with MDD patients not currently experiencing an episode. Therefore, pharmacological or other types of interventions that are used to treat patients with MDD in order to decrease the number of major depressive episodes or delay their occurrence have the potential to translate into large cost reductions.

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Economic burden of depression on society

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Major depressive disorder (MDD) is a mental disorder that frequently affects individuals of all ages. Patients may experience a single episode or recurrent ones. The impact the disease has on an individual’s everyday life is important, resulting in a substantial economic burden imposed on society, with the majority of the costs being generated outside the health care systems. Several cost-of-illness studies on major depression focus on the direct medical, and in some cases, direct nonmedical costs. Indirect costs are not frequently assessed even if they impose a significant burden on society, particularly during the acute phases of the disease. Pharmacological treatment is an important component of direct medical costs, estimated to account for 6% to 29% of total direct health care costs. Major depressive episodes represent an additional burden for society due to increased costs imposed on the health care system and higher productivity losses when compared with MDD patients not currently experiencing an episode. Therefore, pharmacological or other types of interventions that are used to treat patients with MDD in order to decrease the number of major depressive episodes or delay their occurrence have the potential to translate into large cost reductions.
It is a severely disabling and frequent mood disorder that affects individuals of all ages and has a significant impact on everyday life, and imposes a substantial economic burden on society.

Costs related to major depression are substantial and are borne by both the health care sector and other sectors of society (e.g., costs related to loss of productivity). The costs also vary between countries, due to differences in health care systems, and between studies, due to differences in methodological approaches. This review aims to provide a comprehensive summary of the literature assessing the cost of major depression. This review will also discuss the key drivers and the main differences in the total costing structure of major depression.

**Epidemiology**

A review of epidemiological publications on mental disorders conducted by Wittchen and Jacobi showed that one of the three most prevalent diagnoses among subjects between 18 to 65 years of age in Europe was major depression (median 6.9%, 3.1%-10.1%). The disease had the highest prevalence among women aged 35 to 49 years, with a 12-month prevalence of 12.7%. For all European countries plus Iceland, Norway, and Switzerland, the total 12-month prevalence for both sexes was 8.3% (ranging between 7.4% and 9.2%). This estimation implies that there are 18.4 million people suffering from major depression in Europe every year. Figure 1 gives the 12-month prevalence estimated for all mental disorders.

In the United States (US), the lifetime prevalence estimated by the National Comorbidity Survey–Replication (NCS-R) study for major depression was 16.2%; the 12-month estimate was 6.6%. The findings of this study indicated that the majority of patients were moderately or severely affected by the disease (38.6% and 38% respectively), while 10.4% experienced mild depression, and 12.9% very severe depression.

The European Study of the Epidemiology of Mental Disorders (ESEMeD), a cross-sectional population-based study which included 21,425 noninstitutionalized adults from Belgium, France, Germany, Italy, the Netherlands, and Spain, indicated that the 12-month prevalence of MDEs in the male population was 2.8% compared with 5.3% among women. The lifetime prevalence rates of MDEs were higher for women as well: 17.1% for the female vs 9.4% for the male population. A significant correlation of major depressive disorder exists with various sociodemographic factors. As suggested by the NCS-R study in the US, age, marital status, employment, and income of an individual were all correlated with 12-month and lifetime prevalence of major depression.

Unemployment was suggested to have a causal relationship with depression. The ESEMeD study revealed that unemployed subjects were particularly at risk of depression (odds ratio: 2.96) compared with jobholders.

**Economic burden**

- **Cost-of-illness methodology**
  A cost-of-illness study estimates the costs related to a specific disease and is not a comparison between treatment strate-
gies. In full-scale societal perspective, a cost-of-illness study should include direct costs (medical and nonmedical), informal care (ie, care by relatives), productivity losses due to sick leave (aka indirect costs), and intangible costs.

A cost-of-illness study is most often based on a top-down or a bottom-up approach. The top-down approach starts with the identification of total disease-related costs for a given perspective (eg, health care or societal). These costs are divided by the number of cases for the relevant time period to obtain the cost per incident case. The bottom-up approach starts at the other end with the estimation of the cost per case, which is multiplied by the number of relevant cases. The calculation of costs can either be prevalence-based (costs attributable to all cases in a given period of time) or incidence-based (lifetime costs of new cases which have their onset in a given period).

Bottom-up studies have the advantage of being comprehensive and can provide reliable information on utilization of health care resources and productivity losses; however, they require more time and resources, and often the sample of patients included in the study is not representative of the entire disease population. Top-down studies have the advantage of being less complicated and time consuming to conduct; however, cost estimations derived from these types of studies usually lack important components as not all cost categories (eg, nonmedical costs and productivity costs) are included in the aggregated information for health care expenditure.

**Costs of major depression**

The cost-of-illness studies for major depression that this review has identified were conducted using different perspectives, study designs, and methodological approaches in different countries. These variations among the studies resulted in differences in the total cost estimates of depression. Below follows a short summary of the most relevant studies. All studies used the bottom-up approach to collect information related to the burden of major depression.

The Longitudinal Investigation of Depression Outcomes (LIDO) study, was an international cross-sectional observational study that involved primary care patients with depression from six countries; Israel, Brazil, Australia, Spain, Russia, and the United States. Results confirmed that the economic burden of the disease can vary depending on the severity of major depression. For Spain (Barcelona), the mean annual health care costs for patients in remission were lower compared with the costs for patients who were partially in remission or those who were experiencing persistent depression or MDE (€334 vs €874 vs €1335, respectively). Original cost estimates were per month in Spanish prices in the year 2000; they were converted to annual cost estimates in euros (2009 prices) assuming equal resource use per month throughout the year.

Another finding of the study was the difference in costs across participating countries. In Australia, the mean annual health care cost estimates for all patient subgroups were two times

![Figure 2. Working days lost per month due to major depression. Modified from reference 8: Simon et al. Gen Hosp Psychiatry. 2002;24:328-335. © 2002, Elsevier Science Inc.](image-url)
The other 70% of total direct costs was accounted for by outpatient visits, consultations with physicians, emergency department visits, diagnostic tests, pharmacological treatment, and other outpatient costs.

According to a recent observational study in Germany, total annual unadjusted direct costs were € 4821 (2009 prices) for patients being treated for major depression. Inpatient costs (treatment in hospital and rehabilitation centers) accounted for 68% of total direct costs. Total annual indirect costs for the same group of patients were lower than direct costs (€1926, 2009 prices).\textsuperscript{11}

A study that was conducted for the European Brain Council in 2005\textsuperscript{12} combined available published epidemiologic and economic data for European countries plus Iceland, Norway, and Switzerland in order to measure the total cost for different brain disorders. The study showed that the cost of affective disorders (bipolar and unipolar depression) was the highest among the mental disorders, with a total of € 106 billion for all Europe (2004 prices). The population-weighted European annual average cost per case of major depression was estimated at € 3826 (2004 prices), with Germany having the highest cost across all European countries (€ 7102, 2004 prices). For France, the annual average cost per case of depression, which was calculated based on information from the literature, was € 4702 (2004 prices), and for the UK was € 5088 (2004 prices).\textsuperscript{12}

A review of the literature including all available economic evidence for major depressive disorder, conducted by Luppa and colleagues,\textsuperscript{13} suggested that the average annual direct cost due to major depression ranged between US$ 1000 and US$ 2500 (2003 prices), depending on the country in which this cost was measured. Indirect costs accounted mainly for days lost from work and were shown to be between US$ 2000 and US$ 3700 (2003 prices). Differences in all cost components of the direct health care costs can be observed in Figure 3, including the major cost-of-illness bottom-up studies presented in the review of the literature conducted by Luppa et al.\textsuperscript{13} Estimates varied significantly across studies/countries, mainly due to the differences in the characteristics of the study populations and the methodologies used in the studies to measure costs. The study by Hawthorne and colleagues\textsuperscript{13} measured the highest inpatient costs as a percentage of total direct medical costs when compared with the other studies. Pharmaceutical/treatment costs were shown to take almost 30% of total direct medical costs in the study by Trivedi and colleagues.\textsuperscript{13}

In Sweden, a bottom-up cost-of-illness study was conducted by Sobocki and colleagues\textsuperscript{14} to determine the magnitude of the impact of treating depression to full remission. They showed that the total annual per-patient cost for patients with major depression in remission was significantly lower compared with patients on a depressive episode; € 8400 vs € 13800 (2005 prices). Remitting patients had lower direct health care costs and productivity losses compared with those not in remission. For patients in remission, direct health care costs only made up 36% of total costs. Almost the same percentage was applicable for patients undergoing a depressive episode (34% of total costs).\textsuperscript{14} This indicates that the greatest contributor to the burden of disease is productivity losses (indirect costs).

**Treatment cost**

Patients diagnosed with major depression or experiencing a depressive episode are treated with antidepressants, in some cases combined with psychotherapy. Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, escitalopram, fluoxetine, paroxetine, and citalopram, and serotonin norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, are new-generation antidepressants. They are highly prescribed due to their positive impact on the course of the disease and relatively mild safety profile. Nonresponders to one SSRi may continue treatment with another SSRI, with venlafaxine, or switch to the atypical antidepressant bupropion.\textsuperscript{15,16}

A review of the literature by Luppa and colleagues\textsuperscript{13} showed that costs of pharmacological treatment made up 6% to 29% of total direct costs, depending on the methodology and the study population, as well as the year the study was conducted.

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In the cost-of-illness study conducted by Sobocki and colleagues, the total 6-month per-patient cost for antidepressants was €228 (2005 prices), 6% of the total direct health care costs.

An alternative treatment for patients with persistent major depression who do not respond to antidepressant medication, or for severe MDEs, is electroconvulsive therapy (ECT). Pulses of electricity are sent through the brain via two electrodes, usually one on each temple, to induce a seizure while the patient is under a brief period of general anesthesia. The safety of this procedure is controversial since it may cause short- and long-term memory loss, disorientation, headache, and other cognitive disturbances; therefore, it is used mainly for treatment resistant depression.

A Health Technology Assessment (HTA) conducted for the National Institute of Clinical Excellence (NICE) in the UK indicated that the 6-month average cost of treatment with ECT was GBP 1314 (2007 prices). Cognitive Behavioral Therapy (CBT) is another treatment alternative recommended by NICE for managing patients with depression and/or anxiety. It is as effective as pharmacological treatment for treating depression and anxiety, with more lasting effects.

Discussion

Major depressive disorder (MDD) is a mental disorder with a high prevalence, particularly among women. It is characterized by periods when the individual has no/mild symptoms (remission), and by periods when patients experience an exacerbation of symptoms (relapse, MDE). Patients may experience a single episode or recurrent ones. Its impact on the individual's everyday life due to cognitive dysfunction and fatigue is important, resulting in a substantial economic burden imposed on society.

The per capita direct medical cost of major depression (inpatient, outpatient, and pharmaceutical costs), has been shown to be higher compared with anxiety disorders, but lower than psychotic disorders (€7688, 2004 prices), or bipolar depression (€6081, 2004 prices).

All of the cost-of-illness studies reviewed capture the direct medical costs of depression with varying methodological approaches. Nonmedical costs (eg, community services) were considered in a few studies, but there were even fewer studies that took a full societal perspective including informal care and indirect costs (eg, cost of days lost from work or early retirement due to the disease). Indirect costs account for more than half of the total burden of depression. Thus, any study failing to consider these costs will underestimate the true burden depression imposes on society. Working days lost, informal care, and, for more severe cases of depression, community care, are important drivers of the total burden of depression. Since these costs mainly occur outside the health care system, bottom-up cost-of-illness studies that prospectively or retrospectively collect patient-level data are the best approach to fully capture the total cost related to depression.

The pharmacological treatment cost is also an important component of the total costs and was estimated to account for 6% to 29% of total direct health care costs. The differences in health care systems and the year the study was conducted can influence this estimation.

There is also an apparent difference in costs due to whether the patient is in remission or in an acute phase of the disease (MDEs). During remission, direct medical and nonmedical costs, as well as productivity losses, were found to be lower (about 25% to 75% lower) compared with periods in which patients were partially or not in remission (depressive episode).

The costs related to depression also vary between countries, which is not that surprising and can mainly be explained by differences in health care systems and access to care. For example, the total health care costs for patients with an MDE were found to be twice higher in Australia compared with Spain (€2004 vs €1335).

Direct comparison of the findings from the different studies presented in this review is, for the reasons outlined above, not straightforward. What can be concluded is that depression is a costly disease and that it is the acute phases of the disease that are the main driver of the total burden. Therefore, interventions liable to curb the number of MDEs can lead to a substantial reduction in the economic burden for both the health care system and society as a whole.

Consistent and robust evidence shows that the new-generation antidepressants have superior efficacy to the older ones and that they delay potential depressive relapses. It is therefore important for patients to receive antidepressant treatment at an early stage in order to avoid MDEs and reduce the economic burden of depression. However, it has been shown that only a small fraction of depressive patients receive appropriate treatment, while many receive no treatment at all.

A study conducted in Germany indicated that 40% of patients meeting Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria for MDE were not treated at all or received inappropriate interventions. Other treatment alternatives exist for managing the disease: NICE recommends cognitive behavioral therapy (CBT) for the treatment of depression and anxiety as being as efficacious as pharmacological treatments with the advantage of having more long-lasting effects. ECT is a procedure that is used mainly on patients with severe and persistent forms of the disease in which pharmacological interventions have failed to manage the symptoms.
Conclusion

Major depressive disorder is one of the most prevalent mental disorders among adults in Europe, with women being more frequently affected compared with men. Its economic burden is assessed by a number of cost-of-illness studies that show that the time patients with major depressive disorder have to spend off work is the greatest contributor to the burden this disorder imposes on society. Major depressive episodes have a higher economic burden compared with the remission phase of the disorder; therefore pharmacological or other types of interventions that decrease the frequency of depressive episodes have the potential to translate into large cost reductions.

References

Keywords: depression; cost; burden; review; antidepressant; treatment

Le Fardeau socio-économique de la dépression

Le trouble dépressif majeur est une maladie mentale fréquente, touchant les individus de tous âges. Les patients peuvent présenter soit un épisode unique, soit des épisodes récurrents. L’impact de cette maladie sur la vie quotidienne des patients est important, et impose un lourd fardeau socio-économique, la majorité des coûts concernant des domaines autres que celui des systèmes de santé. Plusieurs études de coût du trouble dépressif majeur portent sur les coûts médicaux directs et dans certains cas sur les coûts non médicaux directs. Les coûts indirects, quant à eux, sont rarement étudiés, même si le fardeau économique qu’ils représentent sont conséquents, tout particulièrement au cours des phases aiguës de la maladie. Les traitements pharmacologiques représentent une composante importante des coûts médicaux directs, et sont estimés entre 6 et 29% des coûts totaux liés aux soins de santé. Les épisodes dépressifs majeurs alourdissent encore le fardeau socio-économique en raison des coûts supplémentaires liés aux dépenses imposées aux systèmes de santé et à la perte de productivité, en comparaison avec les coûts concernant les patients dépressifs majeur ne présentant aucun épisode dépressif en cours. Ainsi, les traitements pharmacologiques ou autres mis en œuvre chez les patients ayant un trouble dépressif majeur dans le but d’éviter l’apparition d’épisodes dépressifs majeurs représentent un potentiel certain d’économie importante.
The Question

One of the most challenging issues in managing depression is how to handle the recurrence of a depressive episode that had apparently been successfully treated: should the same antidepressant be given again, or a different one tried? Ten authors from as many countries explore the decision-making process in recurrent depressive episode, taking into account factors such as onset of action, quality of remission, and whether the patient’s general health status has changed since the initial depressive episode.

1. L. Agüera-Ortiz, Spain
2. E. Constant, Belgium
3. M. Di Giannantonio, Italy
4. S. Ivanov, Russia
5. S. Kirli, Turkey
6. D. Lecic-Tosevski, C. D. Miljevic, Serbia
7. K. J. Min, Korea
8. Z. Rihmer, Hungary
9. M. Srisurapanont, Thailand
10. J. Thakore, Ireland

Should the same antidepressant be administered if a depressive episode recurs?
Geriatric depression is a cause of concern to psychiatrists for several reasons. Longer life expectancy has increased the potential for late-life depression, be it late-onset or recurrent. The elderly are also prey to frequent physical comorbidity requiring treatment in its own right. Such factors clearly influence the choice of antidepressant.

The question of whether to use the same antidepressant for a recurrence may have a different answer in a younger patient, but rarely because of comorbidity and comedication. In the elderly, such considerations regularly have to be taken into account and may be crucial in excluding a particular antidepressant even if it has proved effective in the past. Elderly patients with recurrent depression are likely to have received a tricyclic or more recently a selective serotonin reuptake inhibitor (SSRI) for previous episodes.

Thorough medical and cognitive evaluation is mandatory in every new depressive episode. The chosen antidepressant must not compound mild cognitive impairment, let alone dementia. The tricyclic antidepressants and, to a lesser degree, paroxetine, are examples of drugs to avoid in this situation.

Patients with Parkinson’s disease may experience deterioration of their movement disorder if treated with an SSRI. They may be better served by nonserotonergic drugs such as bupropion, agomelatine, mirtazapine, or even a tricyclic. Similarly, in those with arrhythmia treated with drugs such as flecainide, it is best to avoid fluoxetine and paroxetine due to CYP2D6 interaction. Patients on oral anticoagulants such as warfarin or dicumarol should be carefully monitored when adding an antidepressant to their regimen, although the risk of interaction is lower with venlafaxine.

Type 2 diabetics should be monitored for hypoglycemia if they have been started on an SSRI. Many elderly patients become obese, while others lose weight due to concomitant disease. Fluoxetine and mirtazapine are at opposite extremes in terms of their effect on appetite and weight. Hyponatremia is a fairly common adverse effect of many psychiatric drugs, including the SSRIs, especially in the elderly, and symptoms such as mental slowing and drowsiness may be confounded with depression itself. Elderly patients on antidepressants should be regularly monitored in this regard.

Pain is frequent in depressed elderly. Dual inhibitors of serotonin and norepinephrine uptake such as venlafaxine or duloxetine may help such patients. The SSRIs have no pain-relieving properties.

Sexual dysfunction due to antidepressants is too often overlooked in the elderly. Drugs such as bupropion or agomelatine are the least likely to have such an effect.

Insomnia is extremely common in the depressed elderly. Drugs with an activating profile, such as reboxetine or bupropion, may impair sleep. Those with a sedative profile, such as trazodone or mirtazapine, may enhance sleep. Thanks to a unique mechanism of action that normalizes circadian rhythms, the newer antidepressant agomelatine represents a promising option for depressed elderly patients with sleep problems.

In conclusion, treatment choice for recurrent depression in the elderly is often limited by comorbidity and comedication precluding the use of an antidepressant that may have been effective at a younger age. Such factors need to be carefully weighed when selecting treatment for a new episode.

References
should be deconstructed into all its component symptoms and comorbidity. This symptom-based approach will help to identify the appropriate antidepressant based on the brain circuits and neurotransmitters mediating the particular symptoms. For example, a first depressive episode associated with insomnia is probably best treated with a sedative antidepressant. If the recurrence features excessive daytime sleepiness, but not necessarily oversleeping, associated with impaired arousal, alertness and cognition, a different set of brain circuits is likely to be involved. In this case a sedative antidepressant will be less appropriate than an antidepressant that boosts dopamine, norepinephrine, and/or histamine.

A third reason for using a different antidepressant may be that response to the previous antidepressant was only partial. If achieving and sustaining symptomatic remission is an essential first step toward functional recovery, naturalistic treatment studies show that up to two thirds of patients fail to achieve complete remission with the first antidepressant. In such cases, some clinicians employ a number of strategies to optimize treatment: increasing the dosage of antidepressant, switching to another antidepressant, adding a second nonantidepressant agent to augment the effect of the antidepressant, or adding a second antidepressant, typically from another class. But too many patients are allowed to remain in partial remission on their original antidepressant. In this case, it makes sense to change the antidepressant in a recurrence, given that the effect of the original antidepressant was only partial. A drug from a different class may be chosen or another drug from the same class: either choice is legitimate. There is no unequivocal evidence to show the superiority of switching to a different class.

References
3. M. Di Giannantonio, Italy

In psychiatric clinical practice, the choice of suitable antidepressant medication for the treatment of recurrent depressive episodes is an important and controversial topic. Recurrence is generally defined as the appearance of a new depressive episode after at least 6 symptom-free months (remission). However, the clinical definition of remission differs somewhat from that used in therapeutic trials, in which treatment response is usually defined as a decrease in Hamilton or Montgomery-Åsberg Depression Rating Scale scores of at least 50% from baseline. The proportion of trial patients, who displaying significant residual symptomatology after treatment, are considered responders, but not remitters, can be as high as 30%. Incomplete remission of depressive symptoms is associated with increased risk of recurrence and relapse.

Bipolar or unipolar depression?
According to epidemiological studies, the lifetime prevalence of bipolar disorder ranges from 0.8% to 5.1%. The prevalence of treated bipolar disorder has, instead, been found to be lower (0.2%). This discrepancy is possibly ascribable to the fact that many patients are incorrectly diagnosed. The symptoms bipolar patients experience during a depressive episode meet the diagnostic criteria for major depressive disorder. It is, therefore, important to pay particular attention to new clinical findings (e.g., presence of psychotic symptoms, agitation, anxiety, or atypical symptoms), episode severity and suicide risk. The presence of comorbid conditions (e.g., drug or alcohol abuse) should also be considered whenever attempting to achieve complete patient well-being.

No evidence of loss of efficacy on reuse
Recent studies suggest that good responders to an antidepressant drug have a relatively high probability of responding well to reinitiation of the same treatment. In patients with a recurrence after treatment discontinuation, several clinical studies endorse reinitiation of the previously effective antidepressant drug as a first-line strategy. Indeed, the current World Federation of Societies of Biological Psychiatry (WFSBP) guidelines state that, if a full depressive episode recurs during or after treatment discontinuation, the same antidepressant drug at its full therapeutic dosage should be promptly reinstated.

Beyond the clinical response: what other factors?
In addition to the patient’s prior response, the selection of a specific antidepressant depends on various other factors: (i) adverse effects experienced; (ii) changed medical conditions; (iii) use of other nonpsychiatric drugs; (iv) adherence to medication; (v) patient preference; and (vi) pregnancy. Moreover, clinicians must constantly keep in mind that a new depressive episode may potentially constitute a different clinical event as psychiatric symptoms and signs vary greatly both inter-individually and in the same subject at different illness stages. It is, therefore, important to pay particular attention to new clinical findings (e.g., presence of psychotic symptoms, agitation, anxiety, or atypical symptoms), episode severity and suicide risk. The presence of comorbid conditions (e.g., drug or alcohol abuse) should also be considered whenever attempting to achieve complete patient well-being.

References
Choosing drug treatment for a major depressive episode remains a serious problem in modern psychiatry because no single antidepressant currently available ensures successful treatment in 100% of cases. The problem is at its most difficult when dealing with a first depressive episode. It is comparatively easier to choose the most appropriate antidepressant for a recurrent episode because of the guidance afforded by the response to previous therapy.

Clinical experience favors a first-line approach in which a recurrence is treated with the same antidepressant as was used in the original episode, provided it was well tolerated and achieved good quality remission. In most cases this approach is associated with a high probability of response, an optimal risk-benefit ratio, and even good treatment compliance, given the patient’s positive experience in the past.

However, there are some situations in which such an approach could be ineffective or even unacceptable. For example, there is no guarantee that the recurrent episode will be identical to its predecessor in terms of symptoms, severity, and psychiatric comorbidity. Changes in these parameters could well transform an antidepressant that provided a high level of efficacy in the past into a much less effective and even inappropriate agent in the current situation. Thus an antidepressant that had achieved high quality remission from a previous mild depressive episode may well prove ineffective in the same patient if the recurrence involves moderate or severe depression or there is significant comorbidity such as overt anxiety disorder. In such cases, the common temptation is to increase the starting dose, but this carries the risk of poorer tolerability. The alternative is to opt for a different antidepressant that has proved effective in severe depression.

A second possible reason for not automatically reintroducing the previous antidepressant is the presence of somatic comorbidity, manifested or exacerbated after recovery from the previous depressive episode. In such cases there can be additional limitations to choosing an appropriate antidepressant. These include, for example, a high risk of serious complications when using a tricyclic antidepressant in a patient with ischemic heart disease or a selective serotonin reuptake inhibitor in a patient with gastrointestinal disorder. Potentially serious changes in drug metabolism are also possible, especially in the presence of somatic disease per se (in particular of the liver or kidneys). In the polymedicated patient, drug interaction represents another potential danger, since it may significantly alter the tolerability of an otherwise appropriate antidepressant or even flatly contraindicate its use.

Thus, in most cases of recurrent depressive disorder, especially those that are clinically indistinguishable from their predecessor, the most reasonable and useful approach is to choose the previously effective antidepressant. However, in terms of clinical practice it would be interesting and valuable to undertake specific studies designed to test this empirical approach to the treatment of patients with recurrent episodes of depression.
Despite the satisfactory results of drug treatment for major depressive episode, the most appropriate strategy for preventing and treating recurrence remains an important and unresolved clinical issue.

Initial episodes are generally attributed to stressors, whereas those that follow are generally considered spontaneous. Major depressive episode has a recurrence rate of 90% over the subsequent 15 years. Residual symptoms are the only factor unrelated to the patient’s innate characteristics and therefore accessible to intervention. While it is well recognized that complete remission is associated with less recurrence, the relapse rate during the maintenance period is 2% to 4% per month even in patients considered to be in remission, the relapse rate during the maintenance period is 2%

Many studies have shown that sleep disorder and fatigue, concentration difficulties, other cognitive problems, and somatic symptoms are common during the major depressive episode and often continue after treatment. A frequent first-line therapy in such patients, in whom remission appears only partial or who continue to display sleep disturbance, lack of energy, and cognitive difficulties at subthreshold levels despite an apparently satisfactory response, is to add a concomitant drug with a different mechanism of action. For example, sleep disorder and associated fatigue can be relieved by adding a 5-hydroxytryptamine (5-HT2) antagonist to a selective serotonin reuptake inhibitor, although this carries a calculated risk of compounding the cognitive problems.

Despite widespread use of such combination therapies, they have not proved unequivocally superior to switching monotherapies. The current consensus is that different symptoms reflect differences in receptors, chemical transmitter systems, neural cycles, and even intracellular neuromodulatory systems. It therefore makes sense to select drugs targeted at the substructures that subtend specific sets of symptoms. Thus the example, mentioned above, of sleep disorder, fatigue, lack of energy, and cognitive problems, clearly points to the involvement of 5-HT2, melatonin receptors, and dopamine levels in the frontal cortex. In such a case, an appropriate drug might be agomelatine, on the grounds that it ticks every box: not only is it a 5-HT2 antagonist and melatonin receptor MT1/MT2 agonist, it also relieves sleep disorder, enhances cognition by increasing dopamine and norepinephrine levels in the frontal cortex, and at the same time has antidepressant activity.

In conclusion, drugs that have proved safe and effective in previous episodes have long been advocated as the treatment of choice for recurrent depressive episode. But other dimensions should be taken into account for preventing relapse and improving posttreatment quality of life. The very fact that a drug failed to prevent recurrence despite its apparent success in treating the original episode suggests that a different drug may prove a more appropriate option in the longer run.

References
To change or not to change medication is a frequent question in clinical practice. Here we shall discuss two sides of this challenging dilemma. At first glance there is no logical reason not to prescribe the same antidepressant when a new depressive episode occurs in a patient who was a good responder the first time. There are two major reasons in favor of such an attitude. The first is proof of efficacy: the antidepressant that achieved remission the first time has an advantage over any other antidepressant that needs to prove its efficacy. The second is a proof of tolerability: in order to achieve remission the patient needs to take medication for some time, which indirectly points toward absence of significant side effects of the drug. Moreover, clinicians should be aware of patients’ psychological expectations. Patients expect the same drug to work well again and do not understand why they would need a different drug.

On the other hand, there is interindividual variability and complexity in the clinical presentation of depressive episodes, which may reflect differences in biological disturbances (such as distinct subtypes of depressive disorder, ie, typical, atypical, melancholic etc).1,2 A new depressive episode in a patient is not necessarily the same clinical entity as its predecessor. This needs to be taken into consideration when choosing an antidepressant.3 Other factors that could influence the choice of antidepressant include onset of therapeutic activity, and quality of remission (persistence of emotional and cognitive deficits, and negative symptoms, such as anhedonia and psychomotor retardation).4

Although most systematic reviews have shown no significant differences in response rates between antidepressants, there are reports that some antidepressants work more quickly than others. However, there are also reports that some antidepressants are more effective than others, at least in more severe forms of depression.5 The cost of antidepressants might also be important, as well as whether or not they qualify for reimbursement. This is a particular consideration in developing countries where the majority of the population experience chronic psychosocial stress and are poor (which itself can initiate a depressive episode, although this is outside our remit here).

A final consideration is that patients’ health changes over time. They may, for example, develop a somatic disease that rules out the use of a previously effective medication due to its side effects. A special problem concerns the underlying personality traits or disorders, seldom assessed in clinical studies, that can predispose patients to depressive episodes. These frequently shape the clinical picture of depression (atypical, anxious, or borderline depression), or even account for its resistance to treatment.

Depressive episodes must always be treated for long enough (at least 6 months after remission),6 not only to prevent development of recurrent depressive disorder or dysthymia, but also to prevent cumulative morphological and functional changes that can cause cognitive scarring.6

In conclusion, optimized management of depression should be individualized and patient-centered. All relapse risk factors—such as personality vulnerability, type of remission (full, partial), residual symptoms, and psychosocial stressors—should be assessed before deciding to administer a new and different drug or sometimes a combination of drugs. The combination of medication with psychotherapy is a sine qua non as is also the building of a treatment alliance.

References
Over half of patients experiencing an initial episode of major depression will eventually suffer a second. About 75% of those who have had two depressive episodes will have a third. In addition, the more the episodes increase, the shorter the symptom-free interval becomes. Maintenance treatment to prevent further relapse or recurrence is therefore crucial in the management of major depressive disorder. Various treatment guidelines or algorithms recommend maintenance treatment for one or more years to recover full function. Longer-term or even indefinite lifelong prevention may be required.

Unfortunately, not all prophylactic treatments are successful, just as depressed patients sometimes fail to respond to the first antidepressant in the acute situation. There is no doubt that maintenance treatment decreases the risk of recurrence. Nevertheless, depressive episodes may recur after, and even during, the recommended duration of maintenance treatment at the recommended dose.

Several strategies are available for managing recurrence in a patient with major depression. Drug therapy can be administered with the same antidepressant that was effective in the previous episode, or a different antidepressant within the same class, or one belonging to a different class. Other options include the addition of lithium, anticonvulsants, or atypical antipsychotics.

If a depressive episode occurs in a patient already taking an antidepressant as maintenance therapy, the daily dose can be increased. One study of recurrent episode in patients with major depression receiving prophylactic treatment with a selective serotonin reuptake inhibitor (SSRI) found that increasing the same SSRI to the full dose restored euthymia in about 90% of patients. Even though their recurrent episode remitted, 50% of these patients suffered a further episode, but the depressive symptoms were less severe this time than in the index episode. Thus, titration of the current antidepressant is a valuable strategy in managing breakthrough depressive episode. A recent meta-analysis found no difference between switching to a new antidepressant and continuing the same antidepressant for treating the breakthrough episode.

But what strategy should be recommended for patients who experience a recurrence after completing their maintenance treatment? Generally speaking, the first-line approach is to use the same antidepressant that was effective in the previous depressive episode. But if the maintenance treatment was appropriately prescribed, taken at the recommended dose for the recommended duration, with good adherence and apparently complete remission, then it ought to have prevented recurrence. Failure to do so suggests that the maintenance treatment was less helpful than it appeared, meaning that other strategies need to be considered, such as switching to another antidepressant, adding a second antidepressant, or adding a drug that augments the antidepressant effect. There is no hard evidence favoring any one strategy over the other in the drug management of patients with a recurrent depressive episode.

However, some strategies may be more effective than others in individual patients. Clinicians therefore need to approach the problem on a patient-by-patient basis, considering individual factors, such as depression subtype, past and present episode severity, previous response to an antidepressant, number of episodes, family history, psychosocial stressors, comorbidities, bipolarities, treatment adherence, and other recurrence risk factors.

Further reading

– Franchini L, Rossini D, Bongiorno F, Spagnolo C, Smeraldi E, Zanardi R. Will a second prophylactic treatment with a higher dosage of the same antidepressant either prevent or delay new depressive episodes? Psychiatry Res. 2000;96:81-85.
Owing to the biochemical heterogeneity of depressive disorders, groups of depressed patients respond differently to the various antidepressants available. Only about 50% to 60% respond to their first-line antidepressant. However, the differing response patterns to the various drugs are not an exclusive phenomenon since most selective serotonin reuptake inhibitor (SSRI) responders also respond to dual-action (serotonergic and noradrenergic) antidepressants while many depressed patients who fail to respond to their first SSRI respond well to their second. When depressed patients relapse (within the same episode) or suffer a recurrence (a new episode) despite ongoing long-term maintenance antidepressive treatment, ie, when patients suffer breakthrough depression, clinicians face a serious challenge because it becomes impossible to know for sure whether the patient had truly responded to the antidepressant they were given for the original episode. What the clinician took for a “true” antidepressant response may actually have been a spontaneous remission or placebo response. However, breakthrough depression can also be the result of noncompliance or occult physical illness (eg, thyroid dysfunction) in the presence of an authentic antidepressant response. The first step in such cases is to optimize treatment (checking compliance and/or thyroid function, dose escalation, augmentation strategies, etc). This is often successful alone. Should this not be the case, the prior good response to the original antidepressant might have been a virtual response, meaning that a new antidepressant is required, particularly one with faster onset of action and a higher response/remission rate.

The situation is quite different in patients experiencing a new depressive episode (recurrence) several months or years after completing successful antidepressive pharmacotherapy. As there is no evidence that the biochemical background of depression undergoes fundamental changes over time, it is not surprising that clinicians agree (assuming virtual response can be excluded) in recommending for the management of the recurrence the same antidepressant that proved effective in the past. However, this is primarily true for the second or third depressive episode of unipolar major depression because external validators (family history, age at onset, long-term course, etc) show that highly recurrent major depressive episodes (four or more distinct depressive episodes) is evidence of bipolar disease.

The frequency of resistance to antidepressant monotherapy ranges from 41% to 65% in bipolar depression (types I and II combined) and from 18% to 27% in unipolar depression. Bipolar spectrum and bipolar II depressives often show a loss of early and late response to repeated trials of antidepressants (also known as tachyphylaxis) before developing chronic and severe antidepressant-resistant depression. Antidepressant monotherapy in bipolar and bipolar spectrum depressives can worsen the cross-sectional picture of depression not only by causing (hypo)manic switch, but also by inducing or aggravating depressive mixed state/agitation (the major substrate of suicidal behavior). Antidepressant-associated chronic irritable dysphoria (ACID) was significantly more common among bipolar I and II depressives who did, as opposed to those who did not, receive antidepressants. The development of ACID (ie, worsening of depression) was significantly related to a past history of antidepressant-induced mood switches.

On this basis, all major depressives, particularly those experiencing their third or more depressive episode, should be carefully screened for bipolarity. If present, it should be managed with a mood stabilizer or mood stabilizer-antidepressant combination. As for antidepressants, the recommended agent is one such as agomelatine or escitalopram associated with more rapid onset of action, a higher response/remission rate, and fewer hypomanic/manic mood switches.

References

Depression is a clinical syndrome consisting of a lowering of mood tone, loss of interest or pleasure, neurovegetative symptoms, feelings of worthlessness or guilt, and recurrent thoughts of death. This syndrome can be a part of many psychiatric disorders.

To be more specific, the following discussion will mainly focus on major depressive disorder, which is a type of depression contributing substantially to the global burden of disease and disability. The course of major depression is important for treatment planning. For nonpersistent illness with isolated episodes, intermittent treatment courses are probably appropriate. However, for lifelong disease, long-term prophylaxis may be warranted.

The chronic and recurrent nature of depressive symptoms was described almost a century ago, before there was any differentiation between unipolar and bipolar depression. A 10-year naturalistic study of 258 major depressive patients receiving a variety of treatments showed that the average duration of depressive episodes is approximately 5 months, and that none of the sociodemographic or clinical factors seemed to have a consistent influence on the time to recovery. In a 2-year study of those surviving a 3-year trial of antidepressant prophylaxis, depression recurred in 66% of major depressive patients receiving placebo. These items of evidence suggest that depression follows a chronic and recurrent course in most patients.

In contrast to the episodic nature of symptoms, the mechanisms of disease tend to support the hypothesis that neurobiological abnormalities in patients with chronic and recurrent depression are persistent or even lifelong. Gene-environment interactions may predict a person’s risk for major depressive disorder. Recent findings have shown that the combination of the Met allele of brain-derived neurotrophic factor, the short allele of the serotonin transporter, and life stressors increases vulnerability to depression. Structural and functional brain abnormalities in patients with major depressive disorder may be associated with low levels of brain-derived neurotrophic factor, abnormal function of the hypothalamic-pituitary-adrenal axis, and glutamate-mediated toxicity.

A large body of postmortem and neuroimaging studies in depressed patients have reported reductions in grey matter volume and glial density in the prefrontal cortex and hippocampus, both of which regions are thought to mediate the cognitive aspects of depression, such as feelings of worthlessness and guilt. These persistent abnormalities are believed to contribute to recurrent episodes of depression. Such findings suggest that major depressive disorders can be predicted at birth and are likely to persist until the end of life.

In conclusion, the continuity of depression may be viewed in terms of two concepts. From the depressive symptom perspective, clinical depression is a disease with isolated episodes. However, from the standpoint of neurobiological abnormality, major depression, especially the chronic and recurrent form, should be considered as a lifelong disorder. Growing evidence tends to support the latter concept and is leading to wide acceptance of long-term prophylaxis of major depression.

References
The average patient with depression can expect to experience at least four separate episodes each lasting approximately 20 weeks during their lifetime. Or, according to another statistic, 85% of all patients with depression will have a further episode of depression. Recurrence is therefore the norm.

Early onset, index episode severity, a family history of depression, and major psychosocial stressors are the key predictors of recurrence. Residual symptoms and previous episodes are also predictive of future episodes in patients with a history of more than two episodes of depression. Recurrent episodes of depression are characterized by increasing levels of severity, shorter intervals between episodes (cycle acceleration), and a greater number of previous episodes.

Despite such high rates of recurrence, no systematic studies have addressed the problem of exactly which antidepressant to use in a person experiencing their second (or more) episode of unipolar depression. That said, we do know that a trial of the drug eliciting a positive response in the past is a reasonable first choice. However, a larger dose may be needed due to greater severity or perhaps treatment resistance. If no response is seen then a change to another class of antidepressant, combination therapy, or augmentation may be needed. However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed us that such interventions may not be effective, possibly due to the heterogeneous nature of depression. Comorbid medical conditions such as cardiovascular disease and cancer are also common in patients with recurrent depression. These may complicate any pharmacotherapeutic regimen considered in such patients.

Matters are further complicated by the fact that there is little symptom stability between the first and any subsequent episode of depression. For example, if the subsequent episode of depression is atypical in nature, characterized by hypersomnia, overeating, and reversed diurnal variation of mood, then irreversible monoamine oxidase inhibitors have been shown to be more effective than the older tricyclic agents (TCAs), with little or no credible data supporting the use of non-TCA drugs. Furthermore, it is essential to determine whether the subsequent episode of depression is unipolar or bipolar as the pharmacotherapeutic options for the latter are different, as was shown by the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study.

What therefore should we do? We only have clinical practice to guide us and this suggests that provided the subtype of depression is the same as before (eg, unipolar vs bipolar, melancholic vs atypical) and there are no comorbid physical conditions to contend with (eg, cardiovascular disease), then it is best to use the antidepressant the patient responded to in the past.

**References**

Incompletely treated single depressive episodes pave the way for chronic depressive disorder, which has an even stronger negative impact on daily life functioning. Complete remission after a single episode can help prevent the transition to full-fledged chronic depressive disorder. To achieve complete remission, new antidepressants are needed that are capable of addressing all the residual symptoms after the depressive episode has resolved. Valdoxan, the first melatonergic antidepressant, is a totally new approach to depression since it is the first available antidepressant that incorporates a nonmonoaminergic mechanism in its mode of action and treats depression by resynchronizing circadian rhythms. Valdoxan has a novel and distinctive profile of antidepressant efficacy in the short- and long-term management of depression vs placebo as well as vs the most prominent comparators, with an early improvement of symptoms that increases continuously throughout the entire administration period, as described by both patients and doctors. Valdoxan addresses all of the symptoms of depression, including those against which other antidepressants are ineffective, and offers clinical advantages such as weight neutrality, preservation of sexual function, and absence of discontinuation syndrome. Furthermore, results from recent research suggest the absence of emotional blunting after remission. These properties result in a more sustained and complete remission than that observed with conventional antidepressants, thus ensuring better efficacy in the treatment of depression.

One of the major predicaments generated by depression is its contribution to the global burden of disease (GBD). With depression the 4th leading contributor to the GBD, the World Health Organization (WHO) estimated its burden in 2010 to be higher than that of cardiovascular disease and cancer. Community surveys consistently show that the prevalence of major depression is high, and that major depression is strongly associated with disability and impaired functioning and well-being. Depression is the leading cause of years lost to disability (YLDs). By the year 2020, depression is projected to reach 2nd place in the ranking of disability-adjusted life years (DALYs) calculated for all ages and both sexes, a position already achieved today by the age-group 15-44 years.

Depression has a major impact on quality of life and personal as well as work productivity, to the point where these have become the litmus test of antidepressant treatment efficacy. Unfortunately, conventional antidepressants often fail to achieve...
complete recovery and are associated with residual symptoms and high recurrence rates. Recent studies indicate that 2 out of 3 patients receiving a first-line treatment with a selective serotonin reuptake inhibitor (SSRI) will not achieve remission and are at risk for relapse. Incompletely treated single depressive episodes pave the way for chronic depressive disorder, which has an even higher impact on daily life functioning. This transition from single depressive episode to full-blown chronic depressive disorder can occur even with mild depressive symptoms and subsyndromal depression. Thus, whatever the setting, functional remission often remains an elusive therapeutic goal.

Failure of treatment to achieve complete remission of a depressive episode can be explained by a relative mismatch between therapeutics and the pathophysiology of the disorder, which is still only partially understood. The so-called monoaminergic hypothesis, based on the observation of the antidepressant properties of monoaminergic agents, has driven drug development and the treatment of depressed patients for nearly 60 years. However, in recent years, drug development has been taking a new direction in the wake of a greater awareness of the relevance of the core symptoms of depression. Thanks to its novel and distinctive profile of antidepressant action, the recently developed antidepressant agonist and antagonist, which treats depression by resynchronizing the circadian rhythms that are profoundly disturbed in depressed patients, has ushered in a deeper understanding of the pathophysiology of depression (for a review see reference 6).

This article describes the biological basis for Valdoxan’s antidepressant efficacy and highlights its early benefits and additional properties. In particular, studies have shown the favorable antidepressant efficacy of Valdoxan versus SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), and how differs from them clinically in terms of efficacy on the core symptoms of depression, which conventional antidepressants fail to adequately address. Management of depression with Valdoxan is thus much more effective in ensuring complete and sustained remission and preventing a depressive episode from evolving into major depressive disorder.

Valdoxan: a novel and distinctive profile of antidepressant action

Valdoxan, the first melatonergic antidepressant, is the first available antidepressant that incorporates a nonmonoaminergic mechanism in its mode of action, making it a truly novel approach to depression. Valdoxan is a melatonergic (MT1 and MT2) receptor agonist and a 5-HT2C receptor antagonist, which treats depression by resynchronizing the circadian rhythms that are profoundly disturbed in depressed patients.

Circadian misalignment has recently been related to the severity of depression and altered expression of circadian rhythm genes has been observed in individuals with a history of depression. Circadian malfunction is a core feature of depression and disruption of circadian rhythms in depressed patients affects mood, behavior, and physiological and biological functions. Therefore, synchronization of circadian rhythms via pathways affecting the circadian clock and normalizing homeostatic functions promises acute and sustained symptom relief.

The resynchronizing and antidepressant properties of Valdoxan have been described in validated animal models, and previous preclinical research has demonstrated that its antidepressant efficacy is mediated by its action on both the MT1 and MT2 receptors and the 5-HT2C receptors. Behavioral studies, comparing Valdoxan’s efficacy of melatonergic agonists alone or 5-HT2C antagonists alone indicate that the efficacy of amelotamine is grounded in the synergy between the melatonergic (MT1 and MT2) and serotonergic (5-HT2C) receptors: Valdoxan, which acts on both types of receptors, is effective, while melatonin alone or 5-HT2C antagonists alone have no or only a partial effect.

Melatonergic and 5-HT2C receptors are located not only in the suprachiasmatic nucleus, but also in other areas of the brain involved in mood regulation, such as the hippocampus and frontal cortex, and the action of Valdoxan on both types of receptors, favoring their synergy, has recently been characterized at the synaptic and intracellular level in these areas of the brain: treatment with Valdoxan prevents the stress-induced increase in glutamate in rat frontal cortex, unlike melatonin alone and 5-HT2C antagonists alone. Similarly, Valdoxan increases the expression of brain-derived neurotrophic factor (BDNF) in rat frontal cortex and the survival of newly formed cells in the hippocampus, while melatonin alone and 5HT2C antagonists alone have no effect.

Furthermore, melatonergic receptor antagonists abolish the increases in BDNF and cell survival induced by Valdoxan, suggesting that the melatonergic component is necessary, but not sufficient, for the effects of Valdoxan. This synergy has also been observed in the expression of early genes and elements of the intracellular transcriptional pathways. Finally, Valdoxan increases neurogenesis in hippocampus and induces an early maturation of neurons.
Valdoxan: a novel treatment for depressive episodes – Muñoz

Valdoxan treatment therefore activates intercellular and intracellular elements of the brain that appear to cycle in a circadian manner13,15 and which are implicated in the pathophysiology of depression. An overview of the mechanism of the antidepressant action of Valdoxan is given in Figure 1,16 which highlights the resynchronization of circadian rhythms resulting from its unique profile of action—agonist at melatonergic MT1 and MT2 receptors and antagonist at 5-HT2C receptors—acting in a synergistic manner.

Valdoxan: demonstrated favorable antidepressant efficacy in the short and long term

Valdoxan’s novel and original mechanism of action lends it a distinctive profile of antidepressant efficacy, which has been characterized and demonstrated versus placebo as well as versus modern antidepressants. Throughout Valdoxan’s development, studies have consistently evidenced a common denominator that constitutes its unique clinical signature: (i) early and continuous improvement in symptoms; (ii) improvement in all of the core symptoms of depression; (iii) favorable efficacy versus comparators after acute and chronic administration; and (iv) a range of clinical benefits that contribute to the complete and sustained remission observed under treatment.

Antidepressant efficacy versus placebo: first demonstration of early and continuous improvement

Valdoxan’s antidepressant efficacy has been demonstrated in several placebo-controlled studies. Three studies used Valdoxan 25 mg or a flexible dosing of 25 to 50 mg.17-19 These studies reported statistically significant differences vs placebo in 17-item Hamilton Rating Scale for Depression (HAMD17) scores both in the early phases in the treatment, and after the mandatory period of 6-8 weeks, where HAMD17 scores were 2.57, P<0.05; 2.30, P<0.05; and 3.44, P<0.001, respectively for the three studies. A meta-analysis of these studies evaluated the items of the HAMD scale separately and showed that the differences were statistically significant for all of the symptoms of depression: depressed mood; somatic and psychic anxiety; sleep and daytime functioning; and anhedonia, measured by the renewed interest of the patient in performing work and activities. These characteristics of Valdoxan were confirmed in a fourth study at the dose of 25 mg versus placebo,20 where from the first week of treatment the decrease in the HAMD score was significantly more important for Valdoxan than placebo (P=0.005) and remained significant throughout the mandatory period of 8 weeks (P=0.01) (Figure 2). Evaluation of the Maier subscale score showed the significant (P<0.05) improvement in core emotional depressive symptoms with Valdoxan. In all of these studies, Valdoxan was more effective than placebo with respect to the other parameters evaluated (response, remission) and the other scales used (CGI [Clinical Global Impression scale], MADRS [Montgomery-Åsberg Depression Rating Scale]).

Demonstration of efficacy in severely depressed patients is a key criterion for establishing the efficacy of any antidepressant. A pooled analysis of positive placebo-controlled studies, using incremental and nonoverlapping cutoffs of the HAMD scale at baseline from ≥25 up to ≥30, showed that the an-
tidepressant efficacy of Valdoxan was maintained whatever the severity of depression with an effect that was clinically and statistically significant through all the degrees of severity (delta = 3.31, \( P = 0.003 \) and delta = 4.45, \( P = 0.025 \) for cut-offs of 26-27 and 30-33, respectively).²¹

Evaluation of relapse prevention with Valdoxan showed its efficacy in long-term treatment of up to 10 months, with nearly 8 out of 10 patients free of relapse (percentage of relapses with Valdoxan = 21.7% and 23.9% after 6 and 10 months of randomization, respectively, \( P < 0.001 \) vs placebo). This was further demonstration of the distinctive efficacy of Valdoxan, since the survival curve for the patients switched to placebo separated gradually from that of patients continuing on Valdoxan, thus indicating not only the absence of any withdrawal syndrome, but also underlining the different pharmacological action of Valdoxan compared with the survival curves obtained with monoaminergic antidepressants.²²

Antidepressant efficacy versus comparators: confirmation of early improvement and favorable antidepressant efficacy

Valdoxan has been compared with the SNRI venlafaxine and with available SSRIs (sertraline, fluoxetine, escitalopram) both in short-term and long-term treatment. The early improvement with Valdoxan 25-50 mg was observed already by the first week versus venlafaxine (75-150 mg) with an increase in daytime functioning resulting from an improvement in daytime alertness (\( P<0.001 \)) and in the sensation of feeling good (\( P=0.001 \)) as evaluated by visual analog scales.²³ There was also nearly twice the number of responders with Valdoxan (19%) than with venlafaxine (11%, \( P=0.01 \)).²⁴ This favorable action over venlafaxine was sustained after 6 weeks (delta score of 0.32, \( P=0.016 \)) and 6 months (delta = 0.32, \( P=0.025 \)).⁶

With the SSRI sertraline, the early improvement was observed at the second week (first point of evaluation) with twice the number of responders as judged by the HAMD score (20% with Valdoxan 25-50 mg, versus 10.9% with sertraline 50-100 mg, \( P=0.027 \)). These results in favor of Valdoxan were maintained throughout the rest of the study, with a difference in HAMD scores of 1.68, \( P=0.031 \) after 6 weeks and a greater number of responders after 6 months (76% for Valdoxan and 63.5% for sertraline, \( P=0.017 \)).²⁵

A comparative trial with Valdoxan 25-50 mg and fluoxetine 20-40 mg was carried out in a large cohort of severely depressed patients \( n=515 \). CGI scale scores evidenced an early improvement with Valdoxan after 2 weeks of treatment (delta versus fluoxetine = 0.17, \( P<0.035 \)), which continued throughout the treatment. The main end point of the study was treatment efficacy after 8 weeks of treatment using the HAMD, scale, which was shown to be greater with Valdoxan with a significant delta of 1.49, \( P=0.024 \) in favor of Valdoxan (Figure 3).²⁶ This difference can be considered as clinically significant in view of the differences reported in placebo-controlled studies,²⁷,²⁸ and taking into account the fact that fluoxetine is an active comparator.

A similar delta was found in the study versus escitalopram, where 71 patients were randomly allocated to Valdoxan and 67 to escitalopram: after 6 weeks of treatment with Valdoxan 25-50 mg or escitalopram 10-40 mg, the difference in HAMD scores was 1.46, with a standard error of 1.03 in favor of Valdoxan. This clinically significant difference was also statistically significant in terms of noninferiority \( P=0.002 \) with a pre-defined inferiority margin of +1.5.²⁹

The favorable antidepressant efficacy of Valdoxan versus SSRIs and SNRI was confirmed in a pooled analysis of these studies. Over the 6/8-week period, a significant difference in favor of Valdoxan vs active comparators (sertraline, fluoxetine, venlafaxine, escitalopram) was observed, with a total HAMD score of 1.37 (\( P<0.001 \)) and a higher percentage of responders (response was defined as decrease from baseline total score ≥50%) with Valdoxan (71.75%) than with SSRIs/SNRIs (64.52%), with a statistically significant \( P=0.005 \) difference of 7.21% in favor of Valdoxan.³⁰

Early and late clinical benefits of Valdoxan: paving the way for sustained and complete remission

Valdoxan’s tolerability profile is similar to that of placebo, with dizziness (excluding vertigo) being the only adverse event occurring more frequently than with the placebo 6% vs 3.5%, respectively, in the short-term placebo-controlled safety set.⁶ Several isolated cases of reversible transaminase elevations were observed in 1.1% of patients treated with Valdoxan ver-
sus 0.7% in patients on placebo. The difference was not statistically significant and the cases were not associated with any clinical signs. Nevertheless, transaminase determination is recommended at initiation of treatment and periodically thereafter. Even at important dosages, no changes were observed in other biochemical, cardiovascular, or hematological parameters. The number of patients withdrawn due to adverse events was more important with sertraline, fluoxetine, venlafaxine, and escitalopram (10.5% in pooled analysis) than with Valdoxan (6.3%). Other early benefits that ensure good tolerability of Valdoxan is the absence of withdrawal syndrome, as shown in a specific study versus paroxetine. Among the other long-term clinical benefits of Valdoxan are its weight neutrality and its absence of interference with sexual function. In a pooled analysis evaluating 6 months of treatment with Valdoxan or placebo, the change in baseline weight was 0.23 kg with Valdoxan and 0.24 kg with placebo. Lack of interference with sexual function was suggested by the low level of emergent sexual adverse events in the overall safety set during Valdoxan treatment. This was confirmed in a specific study in depressed remitted patients, in which Valdoxan showed a favorable sexual profile in comparison with venlafaxine. To avoid bias due to the disease, these results were corroborated by a specific study in healthy volunteers versus placebo and paroxetine: while no sexual dysfunction was reported with Valdoxan, this was not the case with paroxetine, which differed significantly (P<0.05) from placebo and Valdoxan as early as by the first 2 weeks of treatment.

A recent study assessing emotional processing in healthy volunteers after treatment with Valdoxan 25 mg or placebo showed that Valdoxan improved positive affective memory, decreased subjective ratings of sadness, reduced recognition of sad facial expressions, and reduced the emotion-potentiated startle effect. These early effects on emotional processing in healthy volunteers, which were more specific that those seen with SSRIs, suggest lesser emotional blunting and detachment after remission of depression. This constitutes a distinctive advantage, since these effects, which are detrimental to the quality of life of the remitted depressed patient, are often reported with conventional antidepressant treatment.

Conclusion

The properties of Valdoxan described in this review stem from its resynchronization effect on circadian rhythms, a novel mode of action that confers a distinctively unique clinical efficacy. This efficacy is observed throughout the duration of treatment, and is greater than that achieved by conventional monoaminergic antidepressants. Valdoxan is thus easier to administer for the minimum recommended 6-month duration of antidepressant treatment. Patient adherence to treatment with Valdoxan is stronger than that observed with SSRIs or SNRIs. Clinical experience with Valdoxan has confirmed this distinctive efficacy, since feedback from the patients shows they experience improvement in emotions and social and cognitive functioning (Figure 4) that increases continuously week after week (Figure 5) and is accompanied by early and late clinical benefits. The results from clinical studies show that Valdoxan ensures more sustained and complete remission than the currently available conventional antidepressants, a finding borne out in the naturalistic setting of clinical daily practice.
Keywords: depressive episode; Valdoxan (agomelatine); circadian rhythm; antidepressant; efficacy; pharmacological profile
Le traitement incomplet d’épisodes dépressifs isolés favorise les troubles dépressifs chroniques, dont l’effet sur la vie quotidienne est encore plus délétère. Une rémission complète après un épisode unique peut prévenir le passage à la chronicité avérée. Pour obtenir une telle rémission, il faut de nouveaux antidépresseurs capables de traiter tous les symptômes résiduels qui persistent après la résolution de l’épisode dépressif. Valdoxan, le premier antidépresseur mélatoninergique, constitue une approche totalement nouvelle de la dépression puisque c’est le premier antidépresseur intégrant un mécanisme non mono-aminergique dans son mode d’action et qui traite la dépression en resynchronisant les rythmes circadiens. Le profil de son efficacité antidépressive est innovant et caractéristique que ce soit à court ou à long terme, versus placebo comme versus les plus importants comparateurs : les patients comme les médecins décrivent une amélioration des symptômes précoce et qui augmente de façon continue au cours de la période de traitement. Valdoxan traite tous les symptômes de la dépression, y compris ceux sur lesquels les autres antidépresseurs sont inefficaces, tout en offrant des avantages cliniques à type de neutralité en termes de poids, préservation de la fonction sexuelle, et absence de syndrome de sevrage à l’arrêt du traitement. Des résultats récents suggèrent en outre l’absence d’émoussement émotionnel après rémission. Ces propriétés permettent une rémission plus prolongée et plus complète que celle observée avec les antidépresseurs classiques, donc un traitement antidépresseur plus efficace.
Untreated or inadequately treated somatic diseases are indisputably linked to adverse outcome. This statement, tantamount to a medical principle, curiously tends sometimes not to be thought to apply likewise to psychiatric diseases in general, and depression in particular. This is compounded by the fact that a number of guidelines now recommend a “watchful waiting” approach in the presence of mild-to-moderate depression before pharmacotherapy is instituted. Ever since the introduction of the antidepressants, researchers have been striving to determine which agent(s) and which variables best contribute to a beneficial outcome in depressed patients. Thus attempts have been made to establish the predictive value of demographic, clinical, and biological variables in the outcome of short- and long-term antidepressant treatment. Most data have been obtained retrospectively and concern uncontrolled treatment modalities. These findings indicate that patients suffering from 3 or more episodes of depression, or 2 episodes and additional vulnerability factors are at high risk for relapse/recurrence. Knowledge of these risk factors may help prevent depression from running a chronic course. In addition to demographic, illness, and treatment variables there is still a need to evaluate biological measures (vulnerability factors), for their potential usefulness in helping clinicians determine which patients would stand to benefit from somatic or nonsomatic therapies, whether at the beginning, continuation, and/or maintenance treatment phases.

What are the main categories of predictors of response to antidepressant treatment?

Prospective data concerning clinical predictors of antidepressant treatment response are scarce. In most randomized controlled trials (RCTs), predictors are analyzed post-hoc and not defined at the beginning of the study, because the intent is to establish the efficacy of antidepressant treatment.¹

Most available data are therefore derived from retrospective assessment of the course and outcome of depression.² These predictors include demographic, illness, treatment, and biological variables. Table I (page 188) summarizes the potential predictors of response to antidepressant treatment.

"The high expectations raised by pharmacogenetic investigations in terms of their possible contribution to personalized antidepressant treatment, such as those concerning variations of the serotonin transporter gene, have had to be scaled down due to the relatively large number of associations that were discovered to have only a very small magnitude of effect. It may well be that genetic testing for antidepressant treatment prediction will meet our expectations in the near future, but to date, no genetic test has found its way into clinical practice."
How important are demographic variables in depression?

The influence of age of onset on outcome in antidepressant trials is controversial. In the long-term RCT study of Frank et al., no such association was found. However, previous observations showed that both early onset of depression (under the age of 40 years) and late onset (after the age of 50 years) are associated with a higher risk of recurrence. These diverging results may be explained by the fact that late-onset data have been obtained in clinical populations, whereas the relationship between early onset of depression and higher risk of recurrence was established in a nonclinical population. The latter data were obtained as part of the National Institute of Mental Health (NIMH) Collaborative Study Program on the Psychobiology of Depression (see below). However, some data from clinical populations indicate that an early onset of depression (before age 20) is significantly associated with recurrence.

Bauwens et al. studied the predictive value of psychosocial vulnerability factors within the observation period of 12 months in a sample of unipolar and bipolar patients. Before entry into the study, these patients were stabilized for 6 months with reference to the continuation phase. Unipolar patients were then treated with tricyclics, and bipolar patients with lithium, both in an open-label fashion. The authors found that one of the most robust predictors was adjustment to work, both in the unipolar and in the bipolar groups. In bipolar patients, low degree of social and leisure activities and low degree of self-esteem predicted major and minor recurrences of depression. In unipolar patients, low degree of marital adjustment was associated with recurrences. No such association was reported with life events.

Keitner et al. studied factors associated with 12-month outcome in 28 inpatients with a DSM-III (Diagnostic and Statistical Manual of Mental Diseases, 3rd Edition) diagnosis of major depression. The majority of patients who had recovered by 12 months (49% of total sample) had done so within an average duration of 4.9 months. The five most important factors related to recovery were shorter length of hospital stay, older age at onset of depression, better family functioning, fewer than two previous hospitalizations, and absence of comorbid illness.

Table I. Predictors of outcome of antidepressant treatment and possible factors favoring chronicity of depression

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<td>Occupational status (work adjustment)</td>
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<th>Illness variables</th>
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<td>Family history</td>
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<tr>
<td>Age of onset</td>
</tr>
<tr>
<td>Number of episodes (total, per year)</td>
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<tr>
<td>Duration (cycle, interval)</td>
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<tr>
<td>Begin as mania or depression</td>
</tr>
<tr>
<td>Comorbidity (dysthymia, substance abuse, anxiety disorders, axis II disorder)</td>
</tr>
<tr>
<td>Severity of episodes</td>
</tr>
<tr>
<td>Psychopathology: endogenicity, agitation/retardation, weight change</td>
</tr>
<tr>
<td>Suicidal risk</td>
</tr>
<tr>
<td>Type of onset of individual episode (rapid, slow)</td>
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<tr>
<td>Symptom-free interval</td>
</tr>
<tr>
<td>Measures of adaptive personality functioning</td>
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<tr>
<td>Work adjustment</td>
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<tr>
<td>Leisure activity</td>
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<thead>
<tr>
<th>Treatment variables</th>
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<tbody>
<tr>
<td>Hospitalization</td>
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<tr>
<td>Medication (dosage, duration)</td>
</tr>
<tr>
<td>Timing of treatment in relation to phase</td>
</tr>
<tr>
<td>Number of weeks required for stabilization</td>
</tr>
<tr>
<td>HDRS (average, standard deviation) during maintenance</td>
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<tr>
<td>Type of response (full, partly)</td>
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<td>Additional medication</td>
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<th>Biological variables</th>
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<tr>
<td>Sleep variables (delta sleep ratio)</td>
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<tr>
<td>Neuroendocrine measurements (like DST, fenfluramine challenge test)</td>
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<tr>
<td>Biochemical measurements (like: 5-HIAA, serotonin function)</td>
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<tr>
<th>Pharmacogenetic variables</th>
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In terms of diagnosis it is important to distinguish between single and recurrent episodes. Angst et al. and Lavori et al. showed in natural observation studies that the probability of recurrence is a function of the number of previous episodes. In these studies, the recurrence rate was below 50% when patients experienced one episode. When patients had suffered a second episode, the likelihood of a recurrence was between 50% and 90%, and if patients had a history of 3 or more episodes, the recurrence rate was above 90%. In a placebo-controlled continuation treatment study (6 months) with ami-

**Selected Abbreviations and Acronyms**

- BDNF: brain-derived neurotrophic factor
- NREM: nonrapid eye-movement
- RCT: randomized controlled trial
- REM: rapid eye-movement
- SSRI: selective serotonin reuptake inhibitor
ically useful to predict long-term treatment response. In patients with late-onset depression, male and female relatives with alcoholism and/or sociopathy. Based on the pattern of familial psychosis described by Winokur et al., it was found that relatives had equal rates of depression and there was little association with having female relatives with depression (cycle length (time from the onset of one episode to the onset of the next) was reported as early as 1913 by Kraepelin and later confirmed by Zis, Angst, and Roy-Byrne. These authors found that cycle length has a tendency to shorten with each episode. Specifically, the interval of being well between the first and the second episode was longer than that between each subsequent set of episodes. Further, there is convincing evidence that the greater the number of episodes, the greater the risk of occurrence of another depressive episode (cycle length (time from the onset of one episode to the onset of the next) was reported as early as 1913 by Kraepelin and later confirmed by Zis, Angst, and Roy-Byrne. These authors found that cycle length has a tendency to shorten with each episode. Specifically, the interval of being well between the first and the second episode was longer than that between each subsequent set of episodes. Further, there is convincing evidence that the greater the number of episodes, the greater the risk of occurrence of another depressive episode (cycle length (time from the onset of one episode to the onset of the next) was reported as early as 1913 by Kraepelin and later confirmed by Zis, Angst, and Roy-Byrne. These authors found that cycle length has a tendency to shorten with each episode. Specifically, the interval of being well between the first and the second episode was longer than that between each subsequent set of episodes. Further, there is convincing evidence that the greater the number of episodes, the greater the risk of occurrence of another depressive episode (cycle length (time from the onset of one episode to the onset of the next) was reported as early as 1913 by Kraepelin and later confirmed by Zis, Angst, and Roy-Byrne. These authors found that cycle length has a tendency to shorten with each episode. Specifically, the interval of being well between the first and the second episode was longer than that between each subsequent set of episodes. Further, there is convincing evidence that the greater the number of episodes, the greater the risk of occurrence of another
episode (summarized by Goodwin et al44). As shown by Post35 and Post et al,36 this finding has implications for pharmacological treatment, since, according to the “kindling model,” patients with a higher number of episodes may benefit from carbamazepine rather than from antidepressants or lithium. A further important point, derived from epidemiological data,4 is the finding that the older the patients at the onset of illness, the likelier the early relapses if they were untreated. Age is, however, also reported to be negatively correlated with the likelihood of recurrences.4 Based on these findings it appears that number of prior episodes, psychopathology, and comorbidity are strong predictors of future episodes.

**How do the different antidepressant drugs influence the response to antidepressant treatment?**

New-generation antidepressants, like the selective serotonin reuptake inhibitors (SSRIs) or agomelatine,37 have a lower and more favorable side-effect profile.38 Recent acute and long-term studies indicate that they are as effective as tricyclic antidepressants, at least over the studied time period of 1 year.39 Since the occurrence of side effects is the major reason for patients to discontinue antidepressant medication, it seems likely that these antidepressants have a higher chance of being taken in the long term than antidepressants with an unfavorable side-effects profile, like the tri- or tetracyclic antidepressants. Kupfer et al40 sought whether early treatment intervention in recurrent depression shortened the length of the episode. In a group of 45 patients the authors found that early intervention shortened the overall length of a depressive episode by approximately 4 to 5 months.

The most robust clinical predictor of response to antidepressant treatment seems to be an early onset of clinical changes.41-43 Absence of any change (improvement less than 20%) during the first 2 weeks of treatment was highly predictive of later clinical nonresponse.44,45 Early onset of improvement has been shown repeatedly to be highly predictive of later outcome.44-46 Effective antidepressant treatment initiates clinical changes even during the first week of antidepressant treatment.47,48 Interestingly, use of half-dose antidepressant treatment resulted in a worse outcome than full-dose treatment.49

**What is the status today of biological variables?**

Despite all endeavors to predict clinical response to antidepressant treatments, there is a paucity of biological predictors of antidepressant treatment outcome and no biological method is sufficiently developed to be used in daily clinical practice.50 One of the earliest approaches was the study of electroencephalographic (EEG) sleep variables, as reported by Kupfer et al51 and Frank et al.52 Considerable objective data on sleep changes associated with affective illness were already obtained over 20 years ago, but fewer thereafter.53 The most reliable predictive parameters associated with sleep abnormalities in depression were sleep discontinuity disturbance, diminished slow-wave sleep (delta), shift from slow-wave activity from the first to the second nonrapid eye-movement (NREM) period, shortened rapid eye-movement (REM) latency, and alteration in temporal distribution of REM-sleep. Among these sleep variables, a specific measure termed delta sleep ratio (ratio of average delta wave counts in the first NREM period to average counts in the second NREM period) has been shown to be a strong predictor of short- and long-term outcome in depression. Kupfer et al51 reported that the delta sleep ratio predicted the survival time following discontinuation of interpersonal psychotherapy (IPT-M). Survival time was significantly longer (P<0.05) in patients with a delta ratio >1.1 (95.7±12.4 weeks) compared with the group with a delta ratio <1 (50.4±13.6 weeks). These data suggest that a low delta ratio reflects the “need for pharmacotherapy” in maintenance treatment. Interestingly, there was no clinical characteristic that differentiated the group with a delta ratio of below 1.1, compared with a delta ratio of 1.1 or greater.

**How do the different antidepressant drugs influence the response to antidepressant treatment?**

Probably the most promising approaches concerning biological predictors relate to genetic investigations.54,55 Studies of candidate genes such as the serotonin transporter gene have shown that genetic variations influence the outcome of treatment with SSRIs, but the effects were relatively small56,57 and inconsistent with regard to various ethnic groups. Genetic variations of the norepinephrine transporter gene showed an influence on the outcome of treatment with norepinephrine reuptake inhibitors.58 Brain-derived neurotrophic factor (BDNF)59 and angiotensin-converting enzyme (ACE)60,61 gene polymorphisms seem to be associated with treatment effects with various antidepressants. Pharmacodynamic mechanisms associated with the genetic variants of the drug transporter P-glycoprotein or differential degradation capabilities associated with cytochrome P450 polymorphisms62 may also play a crucial role in the response to antidepressant treatments. Genome-wide association studies in large samples including multilocus analyses also confirmed the multifactorial influence of genetic and clinical variables on the outcome of antidepressant treatment.63,64 Nevertheless, the high expectations raised by pharmacogenetic investigations in terms of their possible contribution to personalized antidepressant treatment have had to be scaled down due to the relatively large number of associations that were discovered to have only a very small magnitude of effect.65,66 Genetic testing for antidepressant treatment prediction may meet our expectations in the near future, but to date, no genetic test has found its way into clinical practice.

The possibility of including imaging studies in genetic paradigms could probably enhance our understanding of biological mechanisms involved in the response to treatment modalities.67 Electrophysiological investigations using, eg, quanti-
Endocrine biomarkers that have been in widespread use for decades, such as those related to the activity of the hypothalamic-pituitary-adrenal axis, studied with the dexamethasone suppression test or the combined dexamethasone/corticotropic releasing hormone (Dex/CRH) test, have not been conclusively proven to be associated with depressed states and relapse probability. These techniques have failed to find their way into clinical routine, in spite of the availability of simplified testing procedures, most probably due to conflicting results concerning a clear prediction of treatment outcomes. Hypothalamic-pituitary-thyroid axis testing showing associations with SSRI response are likewise not used in clinical routine. Interestingly, nocturnal change in thyroid-stimulating hormone and prolactin was associated with response to therapeutic sleep deprivation as a possible indicator of serotonin alteration. Along this line, a psychopathological response, ie, with depression to tryptophan depletion, predicted future depression episodes in seasonal affective disorder.

Brain imaging techniques like regional cerebral blood flow measured with single photon emission computer tomography (SPECT) provide a predictor estimate for SSRI treatment response and regional brain activity in the midbrain measured with positron emission tomography (PET) is correlated with remission after 3 months of SSRI treatment. The availability of serotonin transporter was associated with positive outcome in a recent PET-study. But, again, these methods are not in clinical use.

Are there any specific predictors for chronicity of depression?

Several factors have been found to be associated with chronicity for depression (see also Table II). Chronicity is more likely to develop: if there has been a longer illness episode prior to treatment, in older individuals, in bipolar patients, with psychotic symptoms, with a family history of affective illness, and with premorbid neurotic traits and neuroticism. A worse outcome has been found to be associated with negative life events and absence of social support, whereas positive life events predicted better outcome. Biological markers for chronicity have not shown a consistent pattern. Thus, although persistent dexamethasone nonsuppression at the time of discharge has been shown to predict a greater risk of early relapse, this is not a consistent finding and has not been confirmed by other authors.

Chronicity can also be related to partial remission. This often causes considerable disability and increases the burden on the family. In a follow-up study, Kupfer and Spiker found that approximately one third of inpatients treated with amitriptyline were partial responders. These residual symptoms have also been shown to predict higher relapse and recurrence rates in naturalistic follow-up studies, for instance.

So what conclusion would you draw based on the current understanding of predictive factors in depression?

In integrating the potential methods for the prediction of antidepressant response and the associated concepts, it is important to note that depression is a long-term illness and that it is necessary to determine as rapidly as possible which patients should receive maintenance treatment in order to prevent the development of a chronic course of the illness. Some guidance can be found in the literature, like the survey of Angst et al conducted in over 400 patients and followed up for 20 years. According to this survey, patients experiencing two major episodes within 5 years have a 70% probability of developing two or more episodes during the subsequent 5 years. This has led to the recommendation that a patient should have at least two or three well-defined episodes requiring psychiatric intervention before being treated with maintenance drug therapy. Based on the now existing literature we suggest including other variables to determine which patients are likely to benefit from long-term antidepressant therapy. Table III summarizes the items that would be worth further investigation in future prospective trials.

Table III. Who is likely to benefit from maintenance pharmacotherapy?

| ≥ 3 Episodes |
| 2 Episodes and risk factors |
| Late onset (over 60 years) |
| Early onset (under 40 years) |
| Short interval between episodes |
| Rapid onset of previous episodes |
| Positive family history with affective disorders |
| Comorbidity (double depression, anxiety disorders, substance abuse) |
| Severity of index episode (including suicidality) |
| Poor symptom control in continuation phase |
| Low work adjustment |

Recommendations based on evidence as derived from naturalistic-observational studies and own clinical experience.


DU PREMIER ÉPISODE DÉPRESSIF AU TROUBLE DÉPRESSIF :
QUELS SONT LES FACTEURS DE RISQUE ?

Les maladies somatiques non traitées ou mal traitées évoluent incontestablement de façon défavorable. Cette affirmation, qui équivaut à un principe médical, a curieusement tendance parfois à ne pas être appliquée aux pathologies psychiatriques en général, et à la dépression en particulier. Ceci est aggravé par le fait qu’un grand nombre de directives recommandent maintenant une « attente vigilante » en présence d’une dépression moyenne à modérée avant la mise en place d’une pharmacothérapie. Depuis l’introduction des antidépresseurs, les chercheurs s’efforcent de déterminer les produits et les variables susceptibles de mieux contribuer à une issue favorable pour les patients déprimés. La valeur prédictive des variables démographiques, cliniques et biologiques au cours du traitement antidépresseur à court et à long terme a ainsi été étudiée. La plupart des données ont été obtenues de façon rétrospective et concernent des modalités de traitement non contrôlées. Ces résultats montrent que les patients ayant eu 3 épisodes dépressifs ou plus, ou 2 épisodes et d’autres facteurs de vulnérabilité ont un risque important de rechutes et de récidives. Connaître ces facteurs de risque peut aider à éviter que la dépression ne devienne chronique. En plus des variables démographiques, pathologiques et thérapeutiques, les mesures biologiques (facteurs de vulnérabilité) doivent encore être évaluées, car elles permettraient d’aider les médecins à déterminer les patients pouvant bénéficier de traitements somatiques ou non somatiques, que ce soit au début du traitement, en cours de traitement ou pendant la phase de maintien.
Psychoeducation is an easy-to-administer, time-friendly psychotherapeutic technique aiming at increasing knowledge of patients and caregivers about mental illness, improving disease course through early recognition and treatment of symptoms, and suggesting lifestyle adjustments, problem-solving, and stress-management methods to cope with recurrent psychopathologic disturbances. The ultimate goal of psychoeducation is mitigation of symptoms, prevention of relapses, and achievement of better clinical, functional, and vocational outcomes. In this review, we summarize evidence coming from randomized controlled trials supporting efficacy of psychoeducation in mood—mainly bipolar—disorders. Psychoeducated subjects show better compliance with drug prescriptions, longer time to relapses, fewer recurrences, less time spent ill, and amelioration of functioning when starting from a euthymic state. However, a substantial percentage of subjects may be unwilling or unable to participate in therapeutic sessions, and prophylactic effects of psychoeducation may be more prominent for hypomanic or manic recurrences. Psychoeducation needs to be studied more deeply during acute or subacute mood phases, in standardized and comparable fashion and by independent research groups. Furthermore, given that depression contributes the most to long-term poor outcomes, a specific focus of research on recurrent unipolar and bipolar type II forms of mood disorders is needed. Passive, Web-based psychoeducational approaches have begun to be studied and offer a promising avenue for primary large-scale prevention of affective illnesses.

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Psychoeducation holds particular promise for the early stages of mood disorders. Given that social, family, environment problems, and negative events contribute in a significant way to the pathogenesis of psychiatric diseases, psychoeducation is probably the only intervention with a potential primary and tertiary prophylactic effect regarding risk of relapse and improvement in functioning, respectively. In this context, the possibility of delivering psychoeducation on the Internet has growing appeal.

Depression is one of the major causes of disease burden worldwide and a substantial source of long-term disability. Though great strides in the management of bipolar disorder and unipolar depression have been made since the last few decades, many subjects still fail to respond to treatments, relapse under maintenance therapy, and spend a large amount of their lifetime in a fully or partially symptomatic status, with depression being the major contributor to these discouraging outcomes. Furthermore, poor adherence to psychopharmacologic prescriptions is common among patients with bipolar disorder, with figures ranging from 12% to 64%. Therefore, there is a clear need for alternative approaches other than pharmacologic ones to treat mood disorders. Many psychotherapeutic techniques have proven helpful for depression and especially for bipolar disorder, but they are often not feasible for many individuals due to cost, duration, and the required level of education, self-awareness, and knowledge. Moreover, only in recent years have...
stressed psychotherapeutic procedures become available for research purposes, allowing clarification of their efficacy in different diagnostic categories, clinical settings, degrees of illness severities, and phases of illness course.

In 1991, Harvey and Peet pioneered a psychoeducational approach providing 30 patients attending a lithium clinic with educational videotapes and informative handouts. They demonstrated a significant amelioration in knowledge about and attitudes toward lithium in these subjects in comparison with a control group. Since then, an increasing volume of research has come out while therapeutic techniques as well as methods of investigating their effectiveness have been refined.

Psychoeducation is an easy to administer, time-friendly, and relatively inexpensive psychotherapeutic method, hence it offers the important advantage of possible large-scale application in clinical practice. Table I summarizes fundamental aims of psychoeducational programs supported by the scientific literature, including: (i) giving information to patients, families, and caregivers about mood disorders, so as to improve insight into the illness, reduce stigmatization, and build up a supportive environment; (ii) providing clarification about mechanisms of action of medications, potential side effects, and therapeutic efficacy to favor adherence to prescribed treatment regimens; (iii) emphasizing the importance of a healthy lifestyle (eg, diet, oversuse of caffeine, nicotine, abuse of street drugs, lifestyle regularity in sleep, work, leisure activities, etc) to stabilize the course of illness; (iv) teaching patients early recognition of prodromal and residual symptoms and small signs of mood instability to prevent relapses; and (v) providing stress-management and problem-solving techniques to correct self-perpetuating misbehaviors and cognitive vicious circles. Stress-diathesis and biopsychosocial models are the theoretical framework underlying psychoeducation and assume that mood disorders arise from different pathogenetic contributions such as genetic susceptibility, dysfunctional family environments, stressful life events (especially early life traumas), problems in social interactions, inflexible cognitive styles, and somatic disorders.

In the context of this review we will summarize findings from randomized controlled trials published about individual and group psychoeducation intervention in mood disorders, and discuss current evidence and give hints for future directions of research. Psychoeducation techniques are also implemented in more structured cognitive-behavioral, family or interpersonal psychotherapies. These are beyond the scope of the present work and we refer the interested reader to two recent and thorough reviews.

Randomized controlled trials (RCTs)

Table II lists published RCTs on psychoeducation for mood disorders. To the best of our knowledge Perry et al published the first randomized trial addressing the question of whether teaching patients to recognize prodromes of relapse has prophylactic effects on illness course. In their 18-months follow-up involving 69 bipolar patients—asymptomatic, but with a history of a recent mood episode—the experimental group exhibited a longer time to manic relapses, and fewer of these, as well as better social functioning and employment measures. Yet, the intervention did not affect time to and number of depressive relapses. Possible interpretation of this finding has been provided elsewhere, with for example Lam and collaborators pointing out that patients may find more difficult to recognize and to cope with initial or subtle depressive symptoms. A well-designed Spanish study of psychoeducation found that psychoeducated patients were more compliant with drug prescriptions, as confirmed by higher lithium plasma levels after 2 years follow-up. The study recruited 120 bipolar I and II outpatients in remission for at least 6 months and randomized them to 21 sessions of group psychoeducation plus standard pharmacologic treatment or to treatment as usual plus unstructured “placebo” group meetings, with age and sex matching. The superiority of this design is mainly based on a fair control condition, but also on frequent monthly assessments during the 21-week intervention phase and during the 2-year follow-up. Besides the cited benefit in terms of compliance with treatment, psychoeducated subjects concluded assessments with a significant benefit with regard to number of relapses, time spent without depressive, manic, hypomanic and mixed symptomatology, and number and length of hospitalizations.

The same research group also sought to clarify the efficacy of psychoeducation beyond the improvement of compliance with prescribed medication. Hence, they focused on fully compliant bipolar I patients being euthymic for at least 6 months.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients (N)</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Study design</th>
<th>Results (experimental group vs control group)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>BD, relapse in the previous 12 months, currently euthymic pts (69, 6 BD type II pts)</td>
<td></td>
<td></td>
<td>Training to identify prodromes of the opposite polarities. Rehearsal of an action plan. Diaries. 7-12 sessions of 1 hour each</td>
<td>SB, 18-month follow-up, no &quot;placebo&quot;</td>
<td>Longer time to first manic relapse; 6% vs 31% of pts with manic relapses; no differences in time to and number of depressive relapses; higher dosages of ADs; no differences in compliance with MSs; better social functioning and employment</td>
<td>Perry et al, 1999</td>
</tr>
<tr>
<td>BD type I and II, outpatients in remission for at least 6 months (120), EC: axis I comorbidity, current psychotherapy</td>
<td></td>
<td></td>
<td>EG: 21 sessions of 90 minutes, groups of 8 to 12 pts CG: weekly group meetings of 8 to 12 pts without special instructions (placebo)</td>
<td>Parallel, SB, PC, 20 weeks of treatment, 2 years of follow-up with monthly assessments</td>
<td>26.6% of dropouts from the EG, 11.6% from the CG; 38% vs 60% relapsed during the treatment phase; 67% vs 92% relapsed at the end of follow-up phase; lower total N of episodes and N of depressive episodes; longer time to any, manic, mixed, and depressive recurrence; lower mean N and length of hospitalizations per patient</td>
<td>Colom et al, 2003a</td>
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<tr>
<td>See above. Fully compliant Bipolar I pts (N = 50)</td>
<td></td>
<td></td>
<td>See above</td>
<td></td>
<td>16% vs 56% of pts relapsed during the treatment phase; 60% vs 92% of pts relapsed during the follow-up phase (significant for manic, mixed, and depressive relapses); 0% vs 16% of pts hospitalized during the treatment phase; 8% vs 36% of pts hospitalized during the follow-up phase</td>
<td>Colom et al, 2003b</td>
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<tr>
<td>See above. Sub-analysis of 37 BD type I pts with co-morbid personality disorders</td>
<td></td>
<td></td>
<td>See above</td>
<td>See above</td>
<td>46.7% vs 77% of pts relapsed during the treatment phase; 66.7% vs 100% of pts relapsed during the follow-up phase; longer time to relapse; lower mean N of total, manic and depressive relapses</td>
<td>Colom et al, 2004</td>
</tr>
<tr>
<td>BD I (87%) and II, outpts (306), symptomatic (45% depressed, 34% manic, 21% mixed), severely ill pts (87% hospitalized), comorbidity allowed</td>
<td></td>
<td></td>
<td>Chronic care model: group psychoeducation, practice guidelines, improved access to, and continuity of, care, 5-weekly sessions of 60 minutes during phase I, weekly sessions during phase II.</td>
<td>Effectiveness design, multisite, 3-year follow-up, SB: 24-month follow-up</td>
<td>Lower percentage of weeks in any episode (due mainly to reduction in weeks spent manic); improvement in social functioning (work, parental and extended family role fields); cost-neutral intervention</td>
<td>Bauer et al, 2006</td>
</tr>
<tr>
<td>BD I (77.8%) and II, 22% of pts in remission, 41.5% in a mood episode, 36.2% with sub-threshold symptoms (441), medical and psychiatric comorbidity allowed</td>
<td></td>
<td></td>
<td>Multicomponent. Group psychoeducation, telephone monitoring, optimization of care, crisis intervention. 5-weekly group sessions (phase 1), followed by twice-monthly sessions for the duration of the intervention (phase 2), for a total of up to 48 sessions</td>
<td>Lower mean mania severity scores 19.2 vs 24.7 weeks with manic symptoms No differences in depression ratings</td>
<td>Simon et al, 2006</td>
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<tr>
<td>See above (99)</td>
<td></td>
<td></td>
<td>See above</td>
<td>See above. Prolonged follow-up: 5 years</td>
<td>Longer time to any recurrence; fewer recurrences, effect sizes did not decrease in comparison with the 2-year follow-up results; less time spent ill; Lower median number of days of hospitalization</td>
<td>Colom et al, 2009</td>
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<tr>
<td>BD I and II, outpatients (164), Mean HAM-D scores in EG and CG: 20 and 11; YMRS scores: 7 vs 8. High rates of past hospitalizations and suicide attempts. Few EC.</td>
<td></td>
<td></td>
<td>Collaborative care management, groups of 6 to 8 members, 6-weekly sessions plus optional monthly sessions</td>
<td>12-month follow-up</td>
<td>41.49% of pts participated in 4-6 sessions of psychoeducation; no significant differences in terms of attitudes toward medications, self-reported treatment adherence, symptoms and functioning (significant improvements in both groups)</td>
<td>Sajatovic et al, 2009</td>
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**Table II.** Randomized controlled trial of individual or group psychoeducation for affective disorders.

**Abbreviations:** AD, antidepressant; BD, Bipolar Disorder; CG, control group; EC, exclusion criteria; EG, experimental group; HAM-D, Hamilton Depression Rating Scale; MS, mood stabilizer; N, number; PC, placebo-controlled; pts, patients SB, single blind; YMRS, Young Mania Rating Scale.
and compared 25 patients receiving standard psychiatric care with 25 patients randomized to adjunctive psychoeducation. The intervention group fared better than the control sample both during the 20-week treatment phase (16% of individuals vs 56% fulfilled criteria for any polarity recurrence) and during the 2-year follow-up period (60% vs 92%) with a significantly longer time to relapse and fewer hospitalization needed (0% vs 16% of subjects).

Colom et al subsequently analyzed a subset of the described sample to study the efficacy of psychoeducation in patients suffering from bipolar disorder comorbid with personality disorders. The psychoeducation group consisted of 15 subjects, the majority of whom were diagnosed with a cluster B personality disorder (PD) (ie, 29.7% Borderline PD and 22.7% Histrionic PD) and was compared with 22 control individuals.

A larger percentage of control subjects relapsed during the treatment phase (77% vs 46.7%) and this finding was confirmed at the end of the 2-year follow-up period (100% of controls relapsed vs 66.7% of cases). Survival analyses also showed a longer time-to-relapse for patients receiving psychoeducation. Finally, the latter had a lower number of total, manic, and depressive relapses even if no differences were detected as regards the number of patients hospitalized during follow-up. Although this study shows a significant advantage of psychoeducation plus treatment-as-usual over pharmacologic treatment alone, results were quite discouraging given that all controls and a high percentage of cases relapsed. Yet, authors notice that this was a sample characterized by great overall illness severity, and intervention was not focused on Axis I-Axis II comorbidity. Adjunctive modules of psychoeducation addressing personality disorder issues might further improve outcomes. Recently, Colom and collaborators provided data from the same sample as described above, but with a longer 5-year follow-up, and confirmed previous results. In fact, patients receiving psychoeducation exhibited longer time to any recurrence, fewer recurrences, less time spent ill, lower median number of days of hospitalization, and effect sizes did not decrease in comparison with the 2-year assessments.

A further analysis of collected data provided preliminary evidence that psychoeducation may be useful in subjects diagnosed with bipolar disorder type II. Actually, prior work on mixed bipolar samples did not provide distinct analyses of bipolar type II subgroups. The psychoeducated group (N=7), compared with the control sample (N=10), showed significantly better outcomes in terms of number of any type of recurrences, time spent in mood episodes, and achieved level of global functioning. No differences were found in the number of patients needing hospitalization during follow-up. As usual in bipolar II disorder, at baseline assessment patients presented high rates (40%-50%) of comorbid psychiatric disorders.

However, a study with negative results has been recently published. In this trial, 80 and 84 bipolar I and II patients, respectively, were randomized to a standardized adjunctive psychoeducation program or to treatment as usual. Intervention consisted of 6-weekly interactive group sessions plus optional monthly sessions during a 12-month follow-up phase. Overall, at the beginning of the study, subjects were moderately depressed (mean Hamilton Rating Scale for Depression [HAM-D] score = 18.6±11.3), whereas mean score on the Young Mania Rating Scale (YMRS) was 7.4±5.4, but 32% of patients met criteria for current manic or hypomanic episode. Moreover, a high rate of current or lifetime substance abuse comorbidity was recorded (ie, 87%). The two randomized samples were similar at all follow-up assessments on the majority of outcomes considered: compliance with treatment, psychopathologic measures, and functional status. In contrast, it should be noted that only 49% of patients randomized to psychoeducation participated in 4 to 6 phase I group sessions and fewer than 10% continued attending monthly optional sessions. Secondary analyses restricted to the subgroup effectively receiving the psychotherapeutic intervention demonstrated a significant improvement in attitudes toward medication. This is a partially satisfactory finding, because it highlights the intuitive conviction that compliance with psychotherapy is related to compliance with pharmacologic treatments.

Further to the aforementioned studies of simple psychoeducation that indicate it is a useful treatment in conjunction with pharmacotherapy, other research teams have focused their attention on systematic disease management programs, involving more than a single intervention. These programs have also proved effective in the context of primary care. Below, we summarize results from two of the most interesting trials of multicomponent interventions conducted in bipolar disorder.

Simon et al randomly assigned 441 bipolar I and II patients, in all possible phases of the disease course (ie, remission, threshold, or subthreshold symptomatology), to usual care or to a systematic care program provided by nurse care managers and involving: (i) a collaborative treatment plan (ie, follow-up visits, warning signs of disease worsening or relapse, management of medication side effects, and other coping strategies, identification of a principal care-giver at home); (ii) monthly telephone calls to administer rating scales, check-up on compliance with treatments and tolerability issues; (iii) feedback to treating clinicians and psychotherapists; (iv) 5-weekly psychoeducation group sessions followed by biweekly meetings up to a total of 48 sessions; and (v) crisis management, as-needed support, and coordination with family members. The majority of enrolled subjects (59%) completed at least the first-phase weekly group sessions and 84.9% of individuals agreed to receive at least 12 phone calls. A significant positive effect of the intervention was detected throughout the 24-month follow-up regarding mean mania severity ratings. No differences in depression scores emerged be-
In a 3-year multisite single-blind trial, Bauer et al\(^\text{27}\) randomized 330 subjects to usual care or to a complex intervention including group psychoeducation and reorganization of services to improve access to, continuity of, and monitoring of care. This effectiveness study enrolled, during acute hospitalization, severely ill bipolar I and II patients with few exclusions criteria to best reflect real-world mental health services. This effectiveness study enrolled, during acute hospitalization, severely ill bipolar I and II patients with few exclusions criteria to best reflect real-world mental health services. This effectiveness study enrolled, during acute hospitalization, severely ill bipolar I and II patients with few exclusions criteria to best reflect real-world mental health services. Therefore, prophylaxis of depression should be initiated during euthymic intervals or before disease onset in at-risk populations.

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A substantial heterogeneity in psychoeducation trials design such as diagnosis (eg, bipolar disorder type I, type II, recurrent depression, comorbidity, etc), type of intervention (eg, individual, group, family, psychoeducation alone, or complex chronic care, etc), time of delivering (eg, acute manic or depressive phase, residual symptoms, maintenance phase), stage of the disorder (eg, first episode, early recurrences, chronic stage, rehabilitation) and so on. Table III summarizes variables that should be taken into consideration when planning a trial, but also when interpreting findings from published trials. Psychoeducation seems to be more effective when administered in the context of an euthymic state. Negative results were reported by Sajatovic et al\(^\text{24}\) who randomized patients experiencing acute or subacute episodes. Subjects suffering from prominent symptoms may not profit from psychoeducational aids due to cognitive symptoms, psychomotor disturbances, and/or distorted insight into illness.

Future studies should address more specific questions to distinguish the effectiveness of psychotherapeutic intervention during/after moderate-to-severe depression, mania, hypomania, or subsyndromal states with residual or prodromal symptoms. Moreover, the content of adjunctive modules need to be flexible and appropriate for mood disorders with or without anxiety, substance abuse, eating disorders, and Axis II and medical comorbidities. For example, in a small 2009 randomized trial (N=50), Pibernik-Okanovic and coauthors\(^\text{25}\) reported that psychoeducation benefited subjects with mild-to-moderate depression and suffering from diabetes. At 6-month and 1-year assessments, patients improved both

**Table III.** Heterogeneity of trials of psychoeducation for mood disorders: variables involved.
in terms of psychopathologic measures and indicators of glycemic control, but no significant differences were detected in comparison with a control group merely receiving support and explanations about laboratory monitoring.

Some authors have already suggested that severity and duration of illness, number of episodes, and even sex of participants—with females being more willing to participate—are important variables to take into account when designing a psychotherapy trial. In order to ensure an adequate cooperation of subjects, practical issues such as scheduling of sessions and frequency, individual vs. group formats, intervention limited to patients or extended to family members should be considered as well. In this connection, so far only two studies with negative and positive findings, respectively, have been published, which raise the interesting idea of educating the partners of bipolar manic patients.

Bipolar II patients are particularly prone to depressive relapses and spend much of their lifetime in a full-blown or partial depressive state. Despite a limited sample size, findings published by Colom et al are very promising and warrant larger studies to explore the usefulness of psychoeducation sessions in bipolar II disorder and recurrent unipolar depression. Finally, a particular field of application of psychoeducation techniques is early diagnosis of bipolar disorder, given that depression is the most frequent first presentation of mood disorders. For example, patients could be taught to recognize the early signs of hypomanic/manic activation, particularly if external indicators of bipolarity are present (eg, early onset, family history of bipolar disorder).

**Prevention of mood disorder onset**

Innovative interactive Web-based sessions have been proposed. If they prove helpful, a larger number of patients could be treated in a cost-effective fashion. Indeed, Donker et al have recently carried out a meta-analysis of 5 studies implementing passive psychoeducation approaches (ie, education Web site, weekly telephone calls, personalized mailed feedback or leaflets) for potentially wide populations (ie, community residents, college students, primary care attendees, factory workers). Their findings confirm that psychoeducation has a therapeutic role even as a standalone intervention for subthreshold-to-moderate affective symptoms. Furthermore, its techniques may help prevent severe mood episodes, reduce perceived social stigma, encourage individuals to seek help, integrate different therapies, and teach family members, caregivers, and friends to build up a positive environment around people suffering from psychiatric diseases.

We believe that psychoeducation holds particular promise for the early stages of mood disorders. Given that social, family, environment problems, as well as negative events, contribute in a significant way to the pathogenesis of psychiatric diseases, psychoeducation is probably the only intervention with a potential primary and tertiary prophylactic effect regarding risk of relapse and improvement in functioning, respectively. In 2008, Mackinnon et al reported findings from a large trial showing that at the 12-month assessment, both an Internet-based cognitive behavioral therapy and a depression information Web site were superior to a control condition in relieving depression, as measured by the Center for Epidemiologic Studies–Depression Scale. Through the Web site, participants from the community with high depression scores as main inclusion criterion were provided evidence-based information about symptoms, diagnosis, pharmacologic, psychological, alternative, and lifestyle interventions, as well as contacts to seek mental health aids. The possibility of delivering psychoeducation on the Internet has growing appeal, as it allows mental health providers to exert a positive influence on subjects suffering from initial symptoms of depression and living in environments at risk for depression.

**Conclusions**

Psychoeducation is a patient-centered approach. It offers a significant opportunity to improve mood disorder care and tailor therapies to individual needs. It has shown efficacy in preventing relapses, particularly manic relapses, improving compliance with treatment, and reducing social stigma. Psychoeducated patients develop constructive conflict resolution strategies, learn to assert their needs, and to modulate their affective states, by recognizing worrisome clues of disease reexacerbation and dysfunctional attitudes. More trials from independent research groups and with well-defined designs are warranted. Preliminary evidence is available that psychoeducation may be useful in the early stages of mood disorders. Unfortunately, studies targeting at-risk populations are still scant.


**Efficacité prophylactique de la psychoéducation dans les troubles de l’humeur : acquis et perspectives**

La psychoéducation est une technique psychothérapeutique facile à mettre en œuvre, peu consommatrice de temps, dont le but est d’accroître la connaissance des patients et des soignants sur la pathologie mentale, d’améliorer le cours de la maladie par la reconnaissance et le traitement précoce des symptômes et de proposer des méthodes d’adaptation du style de vie, de résolution des problèmes et de prise en charge du stress pour faire face aux troubles psychopathologiques récidivants. Le but ultime de la psychoéducation est l’allègement des symptômes, la prévention des rechutes et l’obtention de meilleurs résultats cliniques, fonctionnels et professionnels. Cet article passe en revue les données issues d’études contrôlées randomisées confirmant l’efficacité de la psychoéducation dans les troubles de l’humeur, principalement bipolaires. Les patients bénéficiant d’une psychoéducation suivent mieux leur traitement, rechutent dans des délais plus longs, récidivent moins, sont malades moins longtemps et montrent une amélioration de leur activité en période euthymique. Toutefois, un pourcentage important de patients ne veulent ou ne peuvent pas participer à des sessions thérapeutiques, tandis que, par ailleurs, les effets psychopharmacologiques de la psychoéducation peuvent s’avérer en fait plus efficaces dans les récidives maniaces ou hypomaniaques. L’efficacité de la psychoéducation au cours des phases thymiques aiguës ou subaiguës nécessite plus ample évaluation, de façon standardisée et comparable et par des groupes de recherche indépendants. En outre, étant donné que c’est la dépression qui contribue le plus à l’évolution péjorative à long terme, la recherche doit s’intéresser plus particulièrement aux formes récidivantes unipolaires et bipolaires de type II des troubles de l’humeur. Des approches psychoéducatielles dites passives, via Internet, sont actuellement à l’étude et semblent très prometteuses dans le cadre de la prévention primaire à grande échelle des troubles affectifs.

**Keywords:** mood disorder; unipolar depression; bipolar disorder; psychoeducation; primary prevention; lifestyle; relapse; recurrence; compliance
Transcranial direct current stimulation in the treatment of depression

by P. B. Fitzgerald, Australia

Transcranial direct current stimulation (tDCS) is a novel noninvasive method for selectively modulating cortical activation. tDCS involves the application of a low-amplitude current to the scalp via cathodal and anodal electrodes. To date it has been shown to affect a range of motor, somatosensory, visual, affective, and cognitive functions. Techniques similar to modern tDCS were first applied to the treatment of depression in the late 1960s. However, with the expansion of medication treatment of depression, there was a loss of interest in the technique. In the last decade there has been a substantial resurgence of interest in tDCS, led by a series of studies demonstrating its brain effects and apparent safety. As tDCS appears to be able to both increase and decrease brain activity depending on the location of the anode and cathode, it appears suitable for the potential treatment of disorders where abnormalities are seen in cortical activity, such as depression. Several sham-controlled clinical trials of tDCS in patients with clinical depression have now been conducted. Several of these trials have demonstrated antidepressant effects despite the trials being of relatively short duration. However, one trial found no difference between active and sham stimulation, possibly related to the use of a relatively low stimulation dose. In conclusion, tDCS has potential to be developed as a highly novel and innovative treatment for patients with depression. However, substantial clinical trials are required to both demonstrate efficacy and explore the optimal parameters for provision of the treatment.

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Depression is a common, disabling, and difficult to treat psychiatric disorder. A substantial proportion of patients with depression do not respond to standard treatment approaches. A range of new brain stimulation technologies are being investigated for their capacity to have therapeutic effects in the treatment of major depressive disorder (MDD).

Repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex (DLPFC) has been evaluated in a series of studies over the last 15 years and has recently been approved for the treatment of depression under certain circumstances by the Food and Drug Administration (FDA) in the United States. Another form of noninvasive brain stimulation is transcranial direct current stimulation (tDCS). The aim of this paper is to review the application of tDCS in the treatment of depression and its therapeutic possibilities.
Depression and its treatment
MDD is a disorder of high prevalence, many patients experience frequent and disabling relapses of their illness, and there is a significant rate of morbidity and mortality. Depression clearly has a highly significant impact on individual patients, health care systems, and society. Despite developments in medication treatments over the last 20 years, a significant percentage of patients, estimated to be approximately 30%, fail to respond to several trials of standard antidepressant medication. A substantial proportion of these patients remain depressed for prolonged periods of time with few therapeutic options. The main treatment option currently available for these patients with “treatment-resistant depression” (TRD), is electroconvulsive therapy (ECT). This is particularly effective in this population, but is complicated by cognitive side effects, need for anesthesia (and the risks of this), and considerable stigma. Many patients refuse to have ECT or refuse to have a second course of ECT despite the success of an initial treatment course, due to the development of cognitive side effects. They may also have general concerns about its effects on the brain or concerns related to the widespread stigma associated with ECT. In addition, ECT is not an ideal treatment for patients with a range of medical comorbidities that complicate the administration of multiple general anesthetics. It may also be problematic in pregnancy or the postpartum period if a patient responds to controls for the pooled data (mean TOL and n-back) AXIAL slices correspond to z=–16, 20, and 48 mm are shown. Reproduced from reference 7: Fitzgerald et al. Hum Brain Mapp. 2008;29(4):490-501. © 2008, Wiley-Liss, Inc.

tDCS is a noninvasive method for the stimulation of the brain, involving the application of a low-amplitude direct electrical current to the brain through stimulating electrodes placed on the scalp (Figures 2 and 3, page 204). The concept of tDCS has a long historical precedent with descriptions of the use of electrical forms of brain stimulation dating back hundreds, if not thousands, of years. A form of stimulation analogous to contemporary tDCS was first envisaged in the 1950s and 1960s. Early research in animals demonstrated that cortical stimulation (within the cortex or under the scalp surface) with an anode would increase neuronal activity, while cathodal stimulation produced opposite effects (see review in 11). These early studies however, suggested that tDCS effects were not homogenous, and that they may be related to the current’s direction in relationship to the orientation of particular nerve cells. Since the relative rediscovery of this technique in the last 10 years, there has been a considerable explosion in tDCS research across cognitive neuroscience, neuropsychology, and more recently psychiatry domains. This research has substantially enhanced our understanding of the technique, its neurophysiological effects, and its potential application in neuropsychiatric disorders.

Mechanism of action
Contemporary tDCS protocols typically involve the application of a 1 mA or 2 mA direct current (DC) for up to 20 minutes between two surface electrodes. These may vary in size, but are commonly =35cm² (5×7 cm). The electrodes are placed

### SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>DC</td>
<td>direct current</td>
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<td>DLPFC</td>
<td>dorsolateral prefrontal cortex</td>
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<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
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<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>HDRS</td>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
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<tr>
<td>tDCS</td>
<td>transcranial direct current stimulation</td>
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<tr>
<td>TMS</td>
<td>transcranial magnetic stimulation</td>
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<td>TRD</td>
<td>treatment-resistant depression</td>
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on the scalp, one serving as the anode and the other as the cathode. Current flows from the anode to the cathode, some being diverted through the scalp and some moving through the brain.\textsuperscript{15}

Anodal tDCS typically has an excitatory effect on the local cerebral cortex, probably by depolarizing neurons. The converse applies under the cathode, likely through a process of hyperpolarization (Figure 4).\textsuperscript{16} The effects of tDCS are often described as subthreshold because stimulation does not result in the specific stimulation of action potentials, but changes the background level of activity and the likelihood that neurons will fire when physiologically stimulated.

The mechanism of action of tDCS has been explored in a number of ways including using the application of various pharmacological agents. For example, sodium and calcium channel blockers eliminate the effects of anodal stimulation, while blocking N-methyl-D-aspartate (NMDA) receptors prevents the long-term effects of tDCS regardless of direction.\textsuperscript{16} The involvement of ion channels has also been supported by studies of the effects of tDCS on cortical activity. Ardolino et al\textsuperscript{17} studied the effects of cathodal tDCS on spontaneous neural activity and on motor responses evoked by stimulation of the central and peripheral nervous system. The authors concluded that the aftereffects of tDCS have a nonsynaptic mechanism of action based on changes in neural membrane function. An alternative approach to understanding the effects of tDCS has used a combination of tDCS and transcranial magnetic stimulation (TMS). In these experiments, tDCS stimulation is applied to the motor cortex, and TMS is used to measure motor cortical excitability and cortical inhibition. For example, Nitsche et al\textsuperscript{14} found that during stimulation, cathodal tDCS reduced intracortical facilitation. Post-stimulation, anodal tDCS increased facilitation and reduced inhibition. The inverse applied for cathodal tDCS. This suggests that tDCS has effects on inhibitory and excitatory neurons in the cortex, and perhaps the sum effect of stimulation depends on the overall balance of tDCS effects on these individual cell populations. Interestingly, anodal stimulation has been shown to have effects on a TMS paradigm referred to as I-wave facilitation. This paradigm is modulated by gamma-aminobutyric acid (GABA)ergic drugs and ketamine, an NMDA antagonist, but not by ion channel blockers.\textsuperscript{18,19} This suggests that synaptic pathways, as well as ion channel processes, may be involved in the action of tDCS.

Interestingly, it has been observed that the effects of tDCS have a number of features in common with other forms of plastic neuronal change. In particular, tDCS effects are depend-
ent on stimulation intensity and duration, appear to be intra-
cortical in origin, and to be dependent on NMDA receptor ac-
tivity. In summary, although the immediate effects of tDCS
appear to be on changing membrane polarization, this seems
to have secondary effects on synaptic activity, altering aspects
of neuronal plasticity for some period of time after the stimu-
lization ends.

From a different perspective, the mechanism of action of tDCS
has been explored using functional neuroimaging (fMRI) tech-
niques. Functional magnetic resonance imaging and PET stud-
ies have been conducted looking at the effects of both anod-
al and cathodal tDCS. However, the results of these studies are
predominately focused on motor cortical stimulation, rather
than stimulation of brain areas relevant to the treatment of
depression, and there has been some inconsistency within
the findings. For example, Lang et al21 using PET found that
both anodal and cathodal stimulation increased underlying
regional blood flow, whereas an earlier fMRI study reported
a decrease in activity with cathodal tDCS and no change with
anodal stimulation.22

It is notable that we now are aware of a variety of factors that
fluence the effects of tDCS that need to be taken into ac-
count in the design of clinical trials. Clearly, tDCS effects are
dependent on whether anodal or cathodal stimulation is ap-
plied to the site of interest. It also appears to be the case that
the orientation of electrodes in regard to each other may also
be important: orientation would affect the direction of the
current induced during tDCS. The direction of this current in
relationship to the orientation of neuronal components is like-
ly to affect the overall degree of change in cortical excitability
produced by the technique. Optimal electrode arrangements
have been established for stimulation of motor cortex, but no
research has explored the optimal parameters for stimulation
of prefrontal regions that are most relevant to depression.
There is also very little knowledge about optimal stimulation
parameters for producing relevant brain effects, in terms of
stimulation intensity and duration. Stimulation in clinical ap-
lications is usually provided at either 1 or 2 mA, but there
are no substantial comparative studies in clinical groups. The
duration of stimulation also varies dramatically from 10 or
20 minutes per day to up to 8 hours per day, with no studies
having compared variations in stimulation periods.

◆ Safety
There are a number of potential safety issues for considera-
tion in the use of tDCS, and our overall knowledge of the safety
of the technique is somewhat limited. The effects of DC stim-
ulation in the brain are determined by the current strength,
duration of stimulation, and the size of the stimulated area.23
The total charge applied to the brain is determined by these
three factors. Nitsche et al have described safe limits for the
total charge of stimulation although these parameters should
be still considered somewhat preliminary.24 The majority of cur-
rently used protocols, which tend to involve a current between
1 and 2 mA applied for 20 minutes or less to an area between
25 and 35 cm², typically fall well within these safety guidelines.

A series of studies have attempted to establish the safety of
tDCS. For example, tDCS has been shown not to elevate
serum neuron specific enolase levels,13 a sensitive marker of
neuronal damage, or to induce brain edema or alterations of
the blood brain barrier and cerebral tissue detectable by mag-
netic resonance imaging (MRI).24 These studies have typically
involved two electrodes placed on the head, with some con-
cerns raised about the possibility of effects if one electrode
it is placed in a noncerephalic position.

In regard to side effects of treatment, the most commonly
reported issue is an irritation or itching under the electrodes
site.25 Skin lesions have been described that are consistent
with superficial burning, but it is also possible that these le-
sions are produced by the shift of electrolytes through the
skin during the tDCS procedure (shifts in “dermal equilibri-
um by DC-iontophoresis under the supraorbital cathode.”26
Headache, fatigue, and nausea have also been reported.25
It has been suggested that electrodes should not be placed
above areas where the skull does not have continuous in-
tegrity, as this could result in substantial increases in intracra-
nial currents. It is also worth noting that although studies have
not yet found substantial safety issues with tDCS, as the
methods of administration can vary widely (for example the
type of electrode, conducting medium, etc) these will require
systematic assessment over time. In addition, long-term safety
studies have not been conducted to date.

tDCS in depression: early studies
The first studies that used tDCS in the potential treatment of
depression were published between 1964 and the mid-1970s.
Application of the technique in depression and other psychi-
atriic disorders stopped for several decades, but was revis-
ited with the conduct of a series of trials in the last 5 years.
There are substantial differences in the technologies and ex-
perimental protocols applied between the two phases of tDCS
research. Perhaps the greatest difference was that the ma-
Jority of these early studies used bilateral anodal stimulation
applied to the frontal area of the brain. A reference electrode
was often positioned away from the brain, for example on the
knee. The authors often proposed that the effects were
through stimulation of the brain stem, and there was no con-
sideration of frontal lateriality differences as has driven much
of the recent research. A number of the early publications
were open-label pilot studies, but several randomized dou-
ble-blind sham controlled trials were conducted. For exam-
ple, Costain et al randomized patients to receive 12 days of
once-dail stimulation or a sham condition.27 A current of
0.25 mA was used and stimulation was provided for the pro-
tracted period of 8 hours per day. Benefits of stimulation were
reported by medical observers, but not by patients them-
selves. A later double-blind trial using similar stimulation parameters did not report any active effects of treatment. However, as later pointed out by Carney et al., there were significant differences between the characteristics of patients in the two trials. Carney et al argued, supported by their clinical experience in the treatment of 119 patients with the technique (which they called “positive polarization”), that tDCS was most suitable for patients with chronic neurotic or atypical depression not responsive to ECT. Carney et al also described the treatment of a group of patients with persistent hypomania using “negative polarization.”

Figure 5. Depression symptom response with active DLPFC, and active occipital or sham tDCS.

Plots showing mood score changes (as indexed by the Hamilton Depression Rating Scale [HDRS] over time); t₀, baseline; t₁, immediately after treatment; t₂, 15 days after end of treatment; t₃, 30 days after the end of treatment. Each data point represents HDRS mean score; error bars indicate standard error of the mean (SEM).

Abbreviations: DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; tDCS, transcranial direct current stimulation.


tDCS in depression: recent research

Interest in the use of tDCS in psychiatry and neurosciences in general was reinvigorated around the year 2000. A series of important studies conducted predominately at Göttingen in Germany demonstrated that tDCS had substantial capacity to change brain activity. These researchers also conducted a series of studies outlining the effects of a variety of stimulation parameters and explored the safety of the technique. These initial studies have led to a dramatic increase in the use of tDCS in a variety of different applications and cognitive neuroscience, neurology, and psychiatry.

The first study that truly explored the potential use of tDCS in depression was published by Fregni et al in 2006. The authors specifically targeted left DLPFC and applied 5 days of anodal stimulation in 10 patients with major depression (randomized to active or sham). A current of 1 mA was applied for 20 minutes per day on 5 alternating days. Four patients in the active group, but no patients in the sham group, met response criteria and there was a significant difference in the reductions in Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores compared with sham stimulation. The same group then conducted a larger sham-controlled trial, this time including 40 medication-free patients with major depression. They were randomized to either anodal stimulation applied to the DLPFC, anodal stimulation applied to the occipital cortex, or sham tDCS. Ten treatment sessions were applied over 2 weeks, this time at 2 mA for 20 minutes per day. The patients in this study, unlike a number of the rTMS studies being conducted, were not treatment-resistant. A significant improvement in depression was seen in the group that received active stimulation of the DLPFC, but not in the occipital tDCS or sham tDCS groups (Figure 5).

Eight out of 21 patients in the active DLPFC group were considered responders to treatment, compared with 2 patients in the sham and no patients in the occipital tDCS group. The benefit of treatment continued during a 30-day follow-up period.

Rigonatti et al have subsequently compared the response to tDCS in this trial with the response to a 6-week course of fluoxetine at 20 mg per day in a nonrandomized comparison. Response to medication treatment was somewhat slower, but of the same magnitude over time. In both of the initial studies of tDCS depression treatment it was well tolerated, with only mild headaches, itching, and transient skin redness reported as potential side effects.

Several studies have now been published exploring the use of tDCS in depression outside of this original group. Ferrucci et al treated 14 inpatients with severe major depression who had been referred for ECT, with left DLPFC tDCS applied at 2 mA, for 20 minutes twice a day for a total of 5 days. Treatment produced a 30% reduction in depression rating scale scores, which persisted up to 4 weeks post-treatment. Attention and verbal working memory were assessed and these did not change across the treatment period. Treatment was well tolerated, without adverse events.

Another group evaluated tDCS with a double-blind randomized study including 40 outpatients with depression. Treatment was provided for five treatment sessions, 3 days per week. Anodal stimulation was provided to the left DLPFC at 1 mA for 20 minutes. Depression scores improved, but there was no difference between active and sham stimulation. There was no evidence of any impairment in cognitive performance produced by tDCS assessed across a range of cognitive functions. One patient committed suicide during the trial, but there was no suggestion that this was related to the experimental treatment. Side effects included skin redness, itching, or tingling at the electrode sites, headache, lightheadedness, and visual changes. Transient hypomania was seen in 1 patient.
It is worth commenting on the method used for the provision of sham treatment in these studies. Most of the clinical trials of tDCS have utilized a sham design where stimulation is turned on as with active treatment, increased to full stimulation intensity, and then turned off after a short period, usually 30 seconds. This is proposed to mimic the initial onset of skin tingling produced with active tDCS, which dissipates rapidly in a substantial proportion of patients, though not all. Integrity of blinding was assessed in the study by Loo et al and appeared to be robust.10

Conclusions

tDCS is a technique for noninvasive brain stimulation that is currently undergoing a period of intensive research and development. There is clear evidence from the neuroscientific studies conducted on tDCS to date that it has substantial capacity to modulate brain activity, most likely through a mixture of nonsynaptic and synaptic mechanisms. This capacity appears to be accompanied by an ability of the technique to modulate a range of brain functions. For example, tDCS has been shown to modulate working memory and other forms of perception and cognition.11

It is less clear what the use of tDCS will prove to be in the treatment of depression. Depression involves a complex network of brain regions where there is aberrant activity. Some of these regions, such as the DLPFC, are potentially amenable to modulation with noninvasive brain stimulation. However, it is difficult to draw firm conclusions from the research applying tDCS in the treatment of depression to date. This applies most strongly to the early studies, as methodological differences in application of the technique have evolved over time. In regard to the recent series of clinical trials, there is certainly promise in the published data to date. However, antidepressant effects of tDCS have not robustly been demonstrated outside of the group that originally published this application. Considering experience with the development of other noninvasive brain stimulation techniques such as rTMS, it is also likely that these initial trials were using doses and treatment durations likely to prove suboptimal. Initial rTMS trials provided 1 week of treatment, but longer periods of stimulation have clearly been shown to have greater and more beneficial effects.1 This may well prove to be the case with tDCS. In addition, it will be critical for future research to define the optimal patient group for this technique. Patients included in several of the trials to date have not been treatment resistant, unlike many of the trials of rTMS. However, if tDCS can be shown to have antidepressant effects in the general population of patients with depression, given its low cost and simple implementation, it may well prove to be a useful treatment in broad patient populations in areas of the world that do not have access to modern pharmaceutical treatments, or other forms of brain stimulation.

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References
The stimulation transcârnienne à courant continu (STCC) est une nouvelle méthode non invasive de modulation sélective de l’activité corticale. La STCC consiste en l’application d’un courant de faible amplitude au niveau du cuir chevelu au moyen de deux électrodes, l’une positive (anode), l’autre négative (cathode). Il est aujourd’hui démontré que cette technique agit sur un ensemble de fonctions motrices, somatosensorielles, visuelles, affectives et cognitives. Des techniques voisines de la STCC actuelle avaient été antérieurement appliquées au traitement de la dépression dans les années 1960. Cependant, avec le développement des traitements médicamenteux de la dépression, cette technique était tombée en désuétude. Ces 10 dernières années, la STCC a été largement remise à l’honneur, grâce à une série d’études démontrant ses effets sur le cerveau ainsi que son apparente sécurité d’emploi. La STCC permettant d’augmenter ou de diminuer l’activité cérébrale selon la localisation de l’anode et de la cathode, elle semble adaptée au traitement potentiel des troubles comportant des anomalies de l’activité corticale, comme la dépression. Plusieurs études cliniques de STCC contrôlées contre « placebo » (mise en place d’électrodes non actives) ont été maintenant conduites chez des patients ayant une dépression à expression clinique. Malgré leur durée relativement courte, plusieurs de ces études ont démontré des effets antidiépresseurs. Cependant, dans une étude, il n’y a pas eu de différence entre la stimulation active et la stimulation « placebo », probablement à cause d’une dose de stimulation relativement basse. En conclusion, la STCC a le potentiel pour être développé comme traitement innovant destiné aux patients souffrant de dépression. Il faut néanmoins d’autres études cliniques pour démontrer son efficacité et déterminer ses paramètres optimaux.

Keywords: depression; transcranial direct current stimulation; prefrontal cortex; rTMS
A TOUCH OF FRANCE

Manet’s gazes
K. Harding Nahum, USA


Manet, the Man Who Invented Modern Art

An exhibition at the Musée d’Orsay (5 April - 3 July 2011)

I. Spaak, France

The Dead Toreador. 1864-5, oil on canvas, 75.9x153.3 cm. The National Gallery of Art, Washington DC, USA. © Widener Collection/Courtesy National Gallery of Art, Washington.
Manet’s gazes

Manet’s complex art can be understood from the point of view of a new developmental psychoanalysis that has derived its ideas from infancy studies as well as the work of Winnicott, Sander, Stern, and the Boston Change Process Study Group. These researchers have found in the earliest intersubjective exchanges with the mother the model for both the formation of the self and the model for later relationships and cognitive life, therefore overturning Freudian drive theory. Manet’s artistic style—comprised of figures with glacial stares, brilliant surfaces of color, the contraction of space—and his constructed persona as a flâneur are both expressions of how he hid and nurtured what seems to be a false self, formed in response to the misattunements of his early life. Developmental psychoanalysis provides a deeper insight into Manet’s gazes.

by K. Harding Nahum, USA

Katherine Harding Nahum received her BA from Sarah Lawrence College, and a PhD from Boston University. She worked as a fiction writer and art critic after college, and since graduate school has taught 19th-century art and 20th- and 21st-century architecture at Boston College as an adjunct associate professor. Her signature courses are seminars on single artists, as well as Psychoanalytic Approaches to Art, an investigation of methodologies for interpreting artists’ work psychologically. Dr Nahum’s essays on Irish art, contemporary women artists, Edvard Munch, and James Ensor have appeared in exhibition catalogues of the McMullen Museum at Boston College. She has published a Festschrift essay on Hoffmann’s Stoclet Tower, and one on Manet in Devenir, a social science journal devoted to infancy studies. In May she will present her paper, Cézanne’s Nature in Florence at the Fifth Annual Conference on Psychoanalysis and Art.

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Manet’s gazes

The unfocused, vacant, sometimes even glacial stares of Manet’s figures in his paintings dominated, assessed, and dismissed the nineteenth-century spectator or critic who, anxious and confused by these misattuned gazes, was also pulled into a web of misattunement. These gazes were expressions of how Manet hid and nurtured what seems to be a false self, formed in response to the misattunements of his early life. Developmental psychoanalysis provides a deeper insight into Manet’s gazes.

Manet’s gazes – Harding Nahum
We see Manet’s ambiguous paintings as complex images of his regard for the old masters—Velázquez foremost among them—as images of the social flux of a new Baudelairean society, and as a pungent record of the nature of his most intimate early experiences.

Velázquez’s paintings formed a model for figural isolation, brilliant flat planes, contraction of space, glacial stares and deadpan expressions—formal elements toward which Manet was predisposed as an artist. The Spanish master’s realist presentation of kings and dwarfs anticipated how Manet wished to present contemporary society as viewed by the flâneur. Furthermore, Velázquez’s honored role within the Spanish court was one that Manet aspired to within the French Salon. If these aims were contradictory, tant pis!

Manet’s qualities of artistic style worked toward a forceful representation of the nature of his inner life, his self.

A developmental psychoanalytic approach to Manet’s style
There have been many psychological interpretations of Manet’s work essentially based on Freudian drive theory, but none based upon developmental psychoanalysis which can be used to relate the art’s “expressive content to [Manet’s] highly elusive personality, [to identify] the meaning of his quotations, [and to grasp] the unity of his œuvre.” Against a background
of Velázquez’s importance to Manet, I will consider the visual elements he uses and the aesthetic decisions he makes in light of emerging formulations from infancy research and developmental psychoanalysis.²

This new psychoanalysis derives its theory from direct, observational studies of infants. Unlike classical theory, developmental psychoanalysis neither constructs a childhood based upon patients’ necessarily distorted memories nor is it based upon a model that assumes pathology. Incipient problems within “stages” of development “[are] illusory and emerge[...] from theoretical, methodological, or clinical needs and biases in conjunction with cultural pressures. It is in the eyes of the beholder, not in the infant’s experience.”³

Research demonstrates that from the beginning humans are social animals. They are innately pulled into intersubjective exchanges with the care-giving environment to form a living system. Repetitions of sleep, feeding, and intimate exchanges become expected, complex and more coherent—making possible regulation of the self and organization within the system. The infant as an organism moves from the biological to the behavioral, and then to a psychological being very quickly. The ideal goal is the achievement of shared states by the dyad, but that is dependent upon the caregiver’s attunement to the infant’s state and its ongoing sequencing. Virtually from the beginning, states have affective dimensions and shape how well state regulation occurs between the pair. This in turn shapes interaction, behavior, and the formation of personality⁴ because, although never exactly the same, interactions are repeated endlessly. From repeated intersubjective exchanges the infant culls what is invariant.⁵ He makes for himself a prototype of interactive experience whereby his developing self is, or is not recognized, whereby his idiosyncratic style of “being-with” and “being-distinct from” is formed.⁶

The gaze as originary

Gazing, the first of the senses to become refined and controlled by the baby, is a potent means of communication with the mother. At birth the baby’s focal length is set at about eight inches, just the right distance to see his mother, and to see her gazing at him as he feeds. They might remain locked in mutual gaze for over thirty seconds or more, three times longer than adults gaze at one another without speech unless they are going to fight or make love.⁷ Gazing as his mother gazes at him is also a means of self-regulation. The baby regulates his state and communication itself by averting his gaze and reestablishing eye contact as he sees fit. An impinging mother who pursues her child with her gaze might be received by the baby turning his head away, falling asleep, or, depending on the intensity of the pursuit, her gaze might be returned by a blank stare, the ultimate guerilla tactic to fend off the impinging interaction. While the blank stare may appear to be a compliance, it actually resists the mother’s intrusion and asserts the infant’s sense of himself, his own will.

If the baby’s gaze is repeatedly greeted with the inert face of a depressed mother, the blossoming of his self is thwarted; he must fall back upon his own inadequate means of recovery and restitution. The infant may provide what he infers his
mother wants—an array of behaviors that amount to his own false self. A false self might succeed in getting from his mother what he needs. Although “children of depressed mothers tend to be curious and intellectually far-ranging, they know they can’t really turn their mother on; they have an emptiness that cannot be filled.”

Manet’s character and his art were composed of dazzling surfaces; his art of surfaces represents a parallel to Manet’s constructed persona. Artistic style encodes and expresses character; behind both is Manet’s actual self.

We know nothing of the unique features of Manet’s early life within a broad picture of an expectable environment for children of the grand bourgeois. His father was a magistrate and civil judge; his mother a social butterfly with a pleasant voice. She sang at the salons she frequented. By all accounts they were close: she adored her son; he “worshipped” her. The real relationship is impossible to detect from these inscrutable terms. Manet, a malleable child, was described as having a “difficult character” when he continued to do poorly in school.

Artists and biographers have described Manet as a witty and elegantly dressed flâneur concerned with style and form in all things, and distinctly unconcerned with contemporary social ills. He was neither self-aware nor given to intimate revelation. When he announced his marriage to Suzanne Leenhoff to his closest friends, Baudelaire and Antonin Proust, they were shocked, never having known of any prior relationship with this woman who came to the marriage with an eleven-year-old son.

Manet’s silence regarding Suzanne reveals the importance of remaining unknown to his friends; it is an act that exposes the nature of his intersubjective exchanges, and actions speak louder than words. To paraphrase Freud, actions are another “royal road” to the unconscious as dreams are.

Comparing self-portraits
Manet’s late Self-Portrait with a Palette (Private Collection, 1879) is one of two painted in that year, the only true self-portraits he ever made. Based on Velázquez’s in Las Meninas, it signified that he had attained a stature like that of the court...
painter’s own in Madrid, a stature he wanted immediately re-
ognized since upon its completion he summoned his friends
to view it. At the time Manet felt good about his own en-
ergetic promotion of his work and his plans for decorations
for the Hotel de Ville, a program that could be compared to
Velázquez’s decorative schemes for Philip IV. The painting
was regarded ambivalently by both his heirs and the public,
however, since it was withheld from view and sold with dif-

Manet wears a voluminous cream-yellow jacket that billows
from narrow shoulders, a black cravat and stickpin, and a
black bowler hat. A drawing of 1869 by Frédéric Bazille shows
that this was his habitual attire when painting and that the
occasion of making his self-portrait did not dictate the attire.
Perhaps dressing as a flâneur helped him create a comfort-
able state of mind by which he knew himself best.

The artists are shown in both self-portraits with brushes and
palettes poised, both in the process of scrutinizing themselves
as they approach the canvas. The paintings appear to have
been executed very rapidly. Although his stylistic development
may have followed that of the master, here using something
like Velázquez’s late borrore technique, Manet’s brushwork
never quite brings the form to resolution. The alla prima brush-
work of the Spanish master creates space within a continu-
um, and, from a certain viewing distance, places coherent,
volumetric forms within that space.

We are aware of hasty brushstrokes describing surfaces, es-
pecially that of the jacket which becomes a large, gold pres-
ence. How rapidly could he have laid in those brushstrokes
if sitters to Manet describe his laborious process of scrap-
ing out and starting over in long painting sessions?

Velázquez draws out his paint to attenuate the sensitive fingers
and merge them with the brush; immersed in the process
of art, he turns back to the canvas, his body rotating in space.
Before our eyes Velázquez enacts a creative process that re-
results in the image we see. Manet’s body is tied parallel to the
picture plane where it remains fastened and static. His flat
figure suggests that Manet gets stuck in process. Perhaps
Manet reasoned that the chaos of brushstrokes
that form his right hand was the equivalence of
motion, process; but the hand pulls apart and
lacks even the integrity of the brush it holds.

Manet felt he had no imagination and required a
specific object from which to paint. His depend-
ence on a model implies that he could get stuck
within the dynamic process of picturing, essen-
tially an interactive process like the flow of a rela-
tionship.

Velázquez’s gaze seems the agent of a discern-
ing mind that is about to reach a conception that
he will execute with his already moving hand;
Manet’s gaze is vacant yet questioning. His face,
beard, tie, and jacket are nearly equivalent sur-
faces, and the dark triangle at the bottom of the
canvas attracts our eye: it sets off four paint-
brushes. The brush the artist holds has sub-
stance—the bristles are loaded with red pigment,
the metal band binds the bristles, the handle lit
along the upper edge gives it broad modeling.
The brushes below have bristles separated from
their handles, their supports. They overlap the
jacket’s edge.

All four brushes are poised over the unbuttoned
jacket, opened to reveal nothing, no body be-
hind. The black triangle is as black as the back-
ground behind Manet’s head; it is background.
There is no vest, no dress shirt in this area to which
our eye is drawn as to a void that is framed by a
yellow coat. Manet’s artistic strategy now seems

Portrait of Emile Zola. 1868, oil on canvas, 146.5x115 cm. Musée d’Orsay,
Paris, France. © Giraudon/The Bridgeman Art Library.
The nature of the gaze

The artistic process of seeing, engaging, remembering, and creating forms on canvas is an act to which is brought the surrounding culture, a life history, even the tension of the artist’s hand. Manet fused art historical fragments into seemingly inept, shallow compositions of color planes. These he marked at the canvas’s surface—making him a modern master.12 Critics responded that his paintings seemed unfinished, had ambiguous forms and insulting content. Yet Manet was his art and form was the message.

The hauteur of Velázquez’s court figures, particularly their gazes, conveyed an acknowledgement of the scrutiny of the viewer who, like Manet’s viewer, was being dominated, assessed, found wanting, and dismissed. Portraits bound for 17th-century royal courts were meant to display power and prestige, but it was odd indeed that Olympia regarded the male viewer in this manner, or that a street singer did. Manet must have considered such figures powerful. For that matter, the dynamic of the gaze as an aspect of the master’s style, and Manet’s emulation of it, recapitulates Manet’s early interactions that later structured his engagement with others. His choice to engage with Velázquez held a memory trace of his early processes.

A series of figure paintings demonstrates the nature of Manet’s intersubjective relations. Along with the qualities of the gaze, they show a flattening of the figure into bold silhouettes of clear color that caught the eye of the salon goer from among dark or “skied” paintings—but that also expressed a freight-

internally logical and psychologically consistent. The disintegrating hand that paints and creates an art of surfaces—so like his flâneur self—falls apart. The dislocation of the bristles from their supports parallels the distance between the unknown self and its constructed overlay of posturing. Manet’s relentlessly superficial self-portrait reveals the artist’s experience of himself as a hollow man with a false self. Manet has transformed the charm of surfaces that hid and disguised his inner life—into his art.

The nature of the gaze

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ed way of “being-with” and “being-distinct from” a starkly imaged other who recalled a prototype. She intrudes and dominates, if she does not overwhelm.

It seems natural to begin with Manet’s mother whose portrait (Madame Auguste Manet, 1863), shows her in mourning. Her set mouth and distant, vacant gaze must reveal the dimensions of her character since it mirrors those qualities of her features in Manet’s double portrait of his parents (1859-60). Manet is seeing and rendering his mother’s gaze as he knows it. The portrait here captures the ancient misattunements of gazing, later experienced empathically by the spectator.

Distancing gazes are by subtle turns cold, blank, dismissive, challenging, aggressive, rejecting, and sometimes paradoxical to the overbearing form—the gaze rejects while the form impinges, as can be seen in Le Déjeuner sur l’Herbe [The Luncheon on the Grass], 1863.

This is also true of The Street Singer, 1862. The figure is shown as imposing, yet utterly still as she emerges from a café, its doors still moving. Wearing a man’s faluche and a fashionable dress beyond the means of an entertainer of her milieu, she holds a guitar, hoists her skirt and cradles cherries wrapped in paper, a task impossible to execute in one gesture. Our eye is led straight to the cherries by the guitar and the black trim of the dress. These form a diagonal that seems to arrest the figure as well. Manet makes a witty juxtaposition of eyes and cherries, for la guigné, sweet cherry, is visually transformed here to suggest guigner, meaning peer, peep, or ogle. Originally Manet had asked an actual singer to pose for him, but she twice refused him, laughing in his face. The rebuff must have recalled earlier ones, in part embodied here in the placard-like figure that cannot be grasped. The figure does not recognize us; her gaze is unfocused and blank. Resisting our searching gaze it sends us stumbling backward out of the picture into a world where real meaning is to be found, and where, as Manet did, we must muster our own resources.

Paul Mantz’s response of 1863 was necessarily hostile because, like other critics, he felt drawn into Manet’s web of misattunement:

Because of an abnormality we find deeply disturbing, the eyebrows lose their horizontal position and slide vertically down the nose like two commas of shadow; there is nothing there except the crude conflict of the chalk whites with the black tones. The effect is pallid, hard, sinister.13

Manet took another critical beating at the 1865 Salon where Jesus Mocked by the Soldiers and Olympia were hung, two paintings characterized by flat, unmodulated surfaces and blank stares. Since his seeking of comfort from Baudelaire was met with scorn, he traveled to Spain to consult with Velázquez.

Returning from Madrid, Manet felt Velázquez’s paintings represented an acknowledgement of his own work; he felt recognized. Now he responded more to the master’s pictures within pictures.

Zachary Astruc’s (1866) blankly staring figure sits in a dark foreground next to a mirrored surface that is the highly lit picture within, and one that forms a complex system of contrasts. The very idea of contrasts suggests a dyad and a relationship within it. Astruc, a critic and painter, sits in darkness, but his hands are highly lit, as are the curtains, the still life objects and the female figure reflected in the mirror to the right. Has
Astruc made these forms? The static foreground still life is a contrast to the mirrored one that seems as if it is growing, and the compressed picture space is juxtaposed to the deep sweep of space implied in the mirror that includes the woman and ourselves.

The painting contained within Velázquez’s painting held an inner meaning, an elevated reality of moral exemplar, myth and art; now Manet is making here and in the Portrait of Emile Zola (1868), representations of the other in the inter-subjective exchange that are enframed within the picture as art. These portraits involved Manet’s meanings. The mirrored image, suggesting the venerable tradition of art as a mirror to life, contains a figure of a woman—not Astruc’s brunette wife—but a sort of muse who has turned her back, and to whom “Astruc” directs his ambiguously blank and perhaps longing gaze. Unconsciously Manet kept pushing toward an understanding of his art and himself. His late and more subtle paintings within paintings—Argenteuil (1874), Chez le Père Lathuille (1879) and A Bar at the Folies-Bergère (1881-82)—depict men who gaze intensely at women—muses—who are tied to the painting within the painting, a massively important one because it almost is the entire painting.

A muse “…can contribute to the coherence of the self [but] alternatively…the self may be surrendered to an idealized muse.” Manet yearns for the coherence the idealized muse might offer him.

Henri Duplay, a painter of military subjects posed for the figure of the flâneur reflected at the right of the mirror in the Bar at the Folies-Bergère. He has drawn so close to Suzon, the barmaid, that his hat brim seems to project over her head and their noses nearly touch. The figure of Suzon who faces us is the isolated, warily gazing and stiff Infanta Margarita of Las Meninas made monumental. Manet has expanded, almost to the limits of the frame, the mirror containing the image of Margarita’s parents, the king and queen who have suddenly appeared in the space before Velázquez’s painting. Manet has replaced their image with a reflection of “tout Paris,” a whole, mixed society. Suzon’s figure, as it is reflected on the right, and as she faces us, is allied with the mirror through the repetitions of blacks and whites and the cold chalky grey-blue of her skirt, all scumbled to indicate the shimmering surface of the mirror. It is a broad, impressionist painting within the painting. Suzon’s reflected figure responds to Duplay’s gaze to confirm her role as muse. As Manet’s and our own surrogate, Duplay peers pleadingly into her face, his raised hand gripping a cane. As Suzon’s reflected figure bends attentively to the flâneur, she fulfills the desired attunement between artist and muse, infant and mother.

It is quite another matter when we see Suzon directly before us. This Suzon, her blankly aversive gaze shifted by millimeters to the left, is depressed, hardly a muse. She draws herself up and pushes toward us the barrier of the marble bar top on which are arrayed the delectable objects that are available to us. These roses, oranges, and gleaming bottles—equivalents to the succulent still lifes in Luncheon on the Grass and The Street Singer—are as sophs to distract us from engaging with her and truly penetrating the painting’s meaning. Suzon does not acknowledge our gaze but casts us back like fish into the oceanic surge of life we see in the mirror. We’re on our own.

Gazing at Manet

The peculiar blank gazes seen in both Manet’s figures and in his own self-portrait probably capture the artist’s own state of mind formed in the intimate exchanges with his caregivers. Such gazes have been used by the infant to ward off emotional intrusion while maintaining a sense of himself, his will, his agency. Yet Manet’s gazes, his essential flâneur stance and his artistic style of color planes poised just at the surface seem to express what amounts to a false self—an array of behaviors to attract the attention of a depressed mother who was both intrusive and absent. Manet’s behavior was designed to avoid being known himself.
L’art complexe de Manet peut être abordé du point de vue d’une nouvelle approche psychanalytique dite développementale, issue des études portant sur les nourrissons et des travaux de Winnicot, Sander, Stern et du Boston Change Process Study Group. Ces chercheurs ont trouvé dans les tout premiers échanges intersubjectifs entre la mère et l’enfant un modèle pour la formation du moi tout autant que pour les relations plus tardives et la vie cognitive, remettant ainsi en question la théorie Freudienne des pulsions. Le style artistique de Manet – comportant des personnages au regard glacé, des surfaces aux couleurs vives, une contraction de l’espace – ainsi que le personnage de flâneur adonné à l’oisiveté qu’il s’était construit, sont tous deux l’expression de la manière dont il dissimulait et entretenait ce qui semble être un moi factice, formé en réponse aux désajustements – ou discordances – (« misattunements ») subis dans son enfance. Les regards des personnages de Manet dominaient, jugeaient, voire « congédiaient » les spectateurs et critiques du XIXe siècle, les entraînant à leur tour dans tout un processus de désajustements les remplissant d’anxiété et de confusion. Certaines parmi les toiles plus tardives de Manet (Argenteuil ; Chez le Père Lathuille ; Un bar aux Folies-Bergère) suivent la tradition des tableaux en abyme en rapport avec un modèle moral ou d’art noble. Le tableau à l’intérieur du tableau représente ainsi une Muse qui prêterait toute son attention à l’artiste. Dans Un bar aux Folies-Bergère, la serveuse présente deux images de la même femme : celle en abyme, qui est « ajustée », regardant le client droit dans les yeux, l’autre dont le regard fait que le client – et nous – n’avons qu’une envie, celle de partir en courant.

References
2. Developmental Psychoanalysis refers to an emerging system of ideas based on empirical studies of early development by psychoanalytically informed researchers, theorists and clinicians. Some of these writers are Beebe B and Lachmann FM, The Boston Change Process Study Group, P. Fonagy, and J. Lichtenberg.
5. Workshop with Daniel Stern, Children’s Hospital, Boston, October 1, 1994.
Manet was charming, attractive to women, and to his models and friends. Most certainly though he was not the frivolous character that some made him out to be. A studio painter, Manet openly proclaimed his admiration for the great masters and worked alone while admiringly depicting what was new in his time. He never stopped inventing, provoking, or reflecting the sensuality of the world that surrounded him. At his funeral, Degas is reported to have said “He was greater than we thought.”

Seldom has a painter been as decried and mocked during his lifetime as Édouard Manet. Whenever he presented his paintings at the Paris Salons, where the exhibited works were supposed to reflect the aesthetic canons of official art, Manet was disparaged, criticized. Le Déjeuner sur l’Herbe (The Luncheon on the Grass) (1863) and Olympia (1863) scandalized the public, outraged by Manet’s disregard for accepted standards of behavior. Critics scoffed at the force of his colors, at his bold perspectives. Yet rarely was an artist so energetically supported by his peers. Painters, writers, and politicians came to the defense of this charming, urbane, determined man. Often considered as a precursor of the Impressionist movement, in which he counted as friends Renoir, Monet, and others, he was above all a solitary painter striving for reality in the intimacy of his studio. In the catalogue of an exhibition organized at his expense on the fringe of the 1867 Salon he wrote “Mr Manet has no intention of overthrowing old methods of painting or of creating new ones. He simply seeks to be himself and not someone else.” Innovative, unfettered by links with any formalism, Manet was the first modernist painter.

“Monsieur Manet is curt, has the last word. He captures his figures vividly, doesn’t shrink before the harshness of nature, invigorates objects by detaching them one from another. His whole being wills him to see by spots, by simple and vibrant flecks.” These words of the novelist Emile Zola appeared in the 7 May 1866 edition of the newspaper L’Événement, in the first of a long series of generally complimentary articles on Édouard Manet (born and died in Paris: 1832-1883). This trenchant tribute to the immense talent of the artist whose Fifer he had just discovered at the 1866 Paris Salon was paid at a time when Manet was under constant attack by the art world for paintings that drew an angry response from chroniclers and public alike at the Salons, those annual displays of artworks intended to convey what in France was deemed to be good pictorial sense. Lola de Valence (1862), Le Déjeuner sur l’Herbe [The Luncheon on the Grass] (1863), Olympia (1863), and The Dead Toreador (1864-1865) engendered controversy because of their subject matter and workmanship, yet Zola was not alone in championing Manet, whose painting was praised by major figures in the arts and public affairs: Delacroix, Baudelaire, Mallarmé, Degas, Monet, Fantin-Latour, Antonin Proust. A precursor of Impressionism, a movement of which he was not part, Manet remained a “revolutionary” throughout his life, the artist of modernity, the “liberator of painting.”

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Manet, the Man Who Invented Modern Art
An exhibition at the Musée d’Orsay
(5 April - 3 July 2011)

by I. Spaak, France
Sarcasm and gibes

Many were the criticisms leveled at Manet over the years. In 1860, his portrait of his parents—Portrait of Monsieur and Madame Auguste Manet—was deemed vulgar, too dark, a depiction of the resignation of an austere upper class couple of Second Empire France after years of married life. In fact, Manet was in no way seeking to idealize intimacy, but rather to capture a moment in time, a social image of an era. It was a clear reference to the Portrait of Monsieur Bertin by Ingres who, wrote Manet, had sought “to symbolize an age.”

Manet was once again at the center of controversy at the Salon des Refusés (Salon of the Rejected) in 1863, when he was accused of transgressing the rules of perspective, and of morality in The Luncheon on the Grass. Manet’s depiction of a naked young woman seated on the grass among trees beside two fully clothed men clashed with the social customs and esthetic canons of the day. Yet through its attention to detail in the splendid still life of the foreground and its simplification of the rest of the composition, this realistic scene firmly placed Manet in a direct line from Gustave Courbet. Upheaval followed at the 1865 Paris Salon. In his Olympia, Manet wittily side-stepped tradition by replacing the faithful little dog of, say, Titian’s Venus of Urbino, by a black cat, fur on end, tail erect, at the foot of a courtesan’s bed. The public was not amused. Not by the cat, and certainly not by the naked young woman reclining on her bed. Nothing was right with this painting. The model’s “livid color,” “the lines drawn in charcoal, her bloodshot and greenish eyes.” Fun was made of the black ribbon around her throat, the lascivious pose, the exaggerated importance given to the flowers (perhaps from a client), to the black maid beside the bed.

What outraged public and critics alike was above all the theme: this modern Venus awaiting a client. “What is this yellow-bellied odalisque, a base model picked up I know not where, who represents Olympia? Olympia? What Olympia? A courtesan, no doubt” wrote Jules Claretie in Le Figaro. There may have been over three thousand canvasses at the Salon, but visitors seemed only to have eyes for Olympia. Laughter too, sniggers and protests. Outraged, some even threatened to take down the picture. Antonin Proust later wrote that Olympia escaped destruction “only because of the precautions taken by the administrators,” who ordered the canvass to be hung.
beyond the reach of canes. “At a height,” wrote Jules Claretie mockingly, “where even lousy paintings are never hung, above a gigantic door of the last room where it was hard to tell whether one was looking at a pile of naked flesh or a pile of linen.”

Manet later wrote that “the insults rained down,” and to his friend Charles Baudelaire, then in Brussels, “I wish you were here my dear Baudelaire. I would have liked to have your opinion of my paintings.” The poet wrote back: “So I have to speak of you again. I have to make every effort to show what you are worth. What you demand is really foolish. They scorn you; the jokes annoy you; they don’t do you justice, etc, etc.

Do you believe you are the first man in this position? Are you a greater genius than Chateaubriand and Wagner? Much scorn was heaped on them. Yet they survived. And so not to swell you with too much pride, I will say that these men are models, and that you, you are just the first in the decay of your art.”

Zola was surprised at being “the first to praise Monsieur Manet unreservedly.” He determined to “lend him a helping hand” and to rebel against the image created of him “as an outcast, an unpopular and grotesque painter.” Addressing the artist, Zola wrote: “Console yourself. You have been set apart, and you deserve to live apart. You don’t think like all those people, you paint according to your heart, according to your flesh, yours is definitely an assertive personality. Your canvasses are ill at ease alongside the foolishness and sentimentality of the time.”

That Olympia is a reference to Velázquez and to Goya’s The Naked Maja is unquestionable. And the pose of Titian’s Venus of Urbino probably inspired that of Victorine Meurent, Manet’s favorite model and an impudent young Olympia. But unlike the young woman of the Venetian master, there is nothing sweet, ideal, or chaste about Victorine. Manet didn’t make of her a symbol in the way the professors at the School of Fine Arts taught, but a young woman of her time. No allegorical alibi. A common prostitute like so many others of the period. “I render the things that I see as simply as possible,” explained Manet. “So, Olympia, what could be more naïve? There’s harshness I am told. It was there, I saw it. I painted what I saw.” For that is the art of Manet. Painting that does without eloquence, an art inspired by a reality rendered with tremendous inventiveness and exemplary spirit, as well as “great brutality, rare vigor, and vivid hues” (Zola).
A revolutionary who admired the old masters

Original it may be, but Manet liked to cultivate his style through reference to the old masters—the Italians Titian, Tintoretto, and above all Veronese, Rubens, the Dutch, and the Spanish, especially Velázquez, “the painter’s painter,” in whom he found his “ideal in painting.” This taste for Spain—theater, flamenco, bullfighting, tragedy—inspired in Manet’s work bright colors, violent blacks, piercing looks, in masterpieces like Lola de Valence (1862), The Spanish Ballet (1862), and Victorine in the Costume of an Espada (1862), And Boy Carrying a Sword (1861), the model for which was eleven-year-old Leon Koëlla-Leenhoff (1852-1927) who often posed for Manet, notably for Soap Bubbles (1867) and Luncheon in the Studio (1868). Leon’s mother was Suzanne Leenhoff, but it is unclear which Manet fathered the child, the painter’s father Auguste or Édouard himself, who married Suzanne in 1863 after Auguste’s death.

Concision and elegance

Manet was accused of making his models look ugly. So it was that when he painted the young wife of one of his friends in the Portrait of Madame Brunet (1860), without disguising the distinctive features of her homely face, she fled in tears on discovering the canvass, which she declined. Manet simply refused the gradations of shadows that were fashionable. His paintings contain nothing precious or sentimental, but instead great poetry and bold perspectives, whether frontal, as in Races at Longchamp, or shifted, as in The Dead Toreador (1864-1865) whose lifeless body is lit as if by a projector against a dark background, lying diagonally across the canvass from bottom right to upper left.

Lola de Valence. 1862, oil on canvas, 123×192 cm. Musée d’Orsay, Paris, France. © Giraudon/Bridgeman Giraudon.

The Dead Toreador. 1864-5, oil on canvas, 75.9×153.3 cm. The National Gallery of Art, Washington DC, USA. © Widener Collection/Courtesy National Gallery of Art, Washington.
“Conciseness in art,” wrote Manet, “is a necessity and an elegance (...). In a figure, seek intense light and dark shade, the rest will follow. ... And then, cultivate your memory, for nature will never give you just information—it’s like a guardrail that stops you falling into triteness. You must always remain the master and do what pleases you. Not a chore! Oh, no, not a chore!” And Manet’s appeal was achieved through unstinting work in the studio, accurate observation of objects, and by following his own path.

**A kindly socialite**

An upper middle-class Parisian, delightful, never pompous or haughty, Manet was charming, attractive to women, and to his models and friends. Most certainly though he was not the frivolous character that some made him out to be. A studio painter, Manet openly proclaimed his admiration for the great masters and worked alone while admirably depicting what was new in his time. He never stopped inventing, provoking, or reflecting the sensuality of the world that surrounded him. At his funeral, Degas is reported to have said “He was greater than we thought.”

Around 35 years of age, Manet was, Zola wrote, “of average height, on the small rather than tall side. Light brown hair and beard; deep and narrow eyes with full of youthful liveliness and ardor; characteristic mouth, thin, mobile, a tad mocking at the corners.” A dandy in love with the world who “finds secret voluptuous delight in the scented and luminous refinement of evenings,” continued Zola. “He is doubtless drawn in by his love of bright and broad colors; but deep within him there is also an innate need for the distinction and elegance that I find in his works.” Zola contrasted the Manet who charmed because of his physique and manners with the depiction by “contemporary wags” of “a kind of ragamuffin, a ridiculous bogeyman.”

Manet was a man-about-town, a keen observer of Parisian life in cafés, at the *Races at Longchamp*—the latest craze among Parisians—at the theater. “I like this existence,” he wrote. “I like the receptions, the noise, the lights, the parties... in a word the colors.” He recreated an atmosphere in a few lines, annotated the drawings, made a new study, and then painted the canvas. As close to reality as possible, but with his way of seeing, his angle, his touch of genius. “A most delicate accuracy between the tones. A somewhat dry charm, penetrating, truly human,” wrote Zola.

*The rapport with his models*

“When I start something,” said Manet, “I tremble to think that models will fail me, that I won’t see them again as often as I would wish or in the conditions that I’d like. They come, they pose, they leave thinking: he’ll finish it on his own. Well actually no! One finishes nothing alone.”

Each figure in *Music in the Tuileries Gardens* (1862) is identifiable as a friend who posed patiently for Manet. As for those in the *Masked Ball at the Opera* (1873), in his quest for realism Manet had them come in groups to his studio.

The situations he depicts are plausible, real. A girl asked to pose as a *Waitress Serving Beer* (1879), fearing she might be propositioned, insisted her fiancé be present, so Manet included him in the foreground, smoking his pipe.
A man of his time, Manet depicted contemporary events—The Execution of Emperor Maximilian (1867), and luminaries of the age—Clémenceau, Zola, Mallarmé, Antonin Proust, and Henri Rochefort, the founder of the newspaper La Lanterne who in 1874 escaped by boat from a penal colony in New Caledonia, where he had been deported for life for supporting the 1871 Paris Commune.

It was a young woman from a good family who would become one of Manet’s most bewitching muses. A friend of Degas, Renoir, and Monet, a painter herself, Berthe Morisot was a member of the large group of Impressionists that Manet rubbed shoulders with. Arranged by their mutual friend Henri Fantin-Latour, the meeting between Berthe and Manet took place in 1868 at the Louvre where she was copying a painting by Rubens. Manet took an interest in Berthe’s work and suggested they meet again. He discovered that she was both passionate and gentle, as well as a “devilish beauty,” especially because of her eyes, which were an intense black, a favorite of the painter, emblematic of his style. Édouard Manet was the painter Berthe most admired among her contemporaries. Sometimes she was inspired by the same subjects; Manet did several portraits of her. Shortly after their meeting, he painted The Balcony (around 1868-1869), a studio composition inspired by Goya’s Majas on a Balcony.


Femme fatale
Berthe Morisot is shown seated, pensive, a closed fan held in interlocking fingers, her right forearm resting on the balcony guard rail. Standing beside her the young violinist Fanny Claus is flirtatious. Behind them stands a man smoking a cigar (another close acquaintance: Antoine Guillemet, a landscape painter).

On leaving the 1869 Salon where Le Balcon was exhibited, Berthe wrote to her sister: “I found Manet, wearing a hat in full sunlight, looking stunned. He asked me to go and see his painting because he didn’t dare move. I’ve never seen such an expressive physiognomy. He laughed, then seemed worried, saying that the picture was very bad, but then adding it was a great success. Decidedly he has a most charming nature which pleases me greatly. His paintings produce as always the impression of a wild, even tart fruit. They are far from displeasing. I am more strange than ugly; it appears that..."
the epithet femme fatale has been circulating among curious onlookers." After *The Balcony*, Berthe posed for Manet more than any other model. Their artistic understanding allowed Manet boldness and freedom, as in the portrait *Berthe Morisot With a Bouquet of Violets* (1872) where she is dressed in black, her hair tousled beneath a black hat, the white neckline of her blouse accentuated by the mauve of the flowers. Paul Valéry would later say "I do not rank anything in Manet’s work higher than a certain portrait of Berthe Morisot dated 1872."

Manet always had a predilection for flowers and fruits, whether in large compositions, such as the mandarin oranges and roses in front of the waitress of *A Bar at the Folies-Bergère* (1881-1882), or as the main subject of his delightful still lifes, such as *Pinks and Clematis in a Crystal Vase* (1882). Peonies, lemons, asparagus, peaches, figs, and grapes are everywhere.

But make no mistake, these are still lifes painted in the artist’s studio, and not in the open air as by his Impressionist friends. It is true Manet on occasion left Paris to paint outdoors, as when he visited his friend Monet at Argenteuil, but it would be a mistake to confuse him with these painters of fleeting impressions. And anyway, it matters little who Manet is confused with. What is important is that he always sought to be true to what he saw, leaving others to say whatever they will.

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**Manet, Inventeur du Moderne**

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Rarement peintre a été aussi sifflé et moqué de son vivant comme le fut Edouard Manet (1832-1883). À chaque présentation de ses tableaux dans les Salons, ces rassemblements d’œuvres censés refléter les canons esthétiques de l’art officiel, le peintre est hué, critiqué. Certaines toiles, telles Le Déjeuner sur l’herbe (1863) et Olympia (1863) allant même jusqu’à provoquer des scandales. Le public crie à l’outrage aux bonnes mœurs, les critiques raillent la force de ses couleurs, l’audace des ses angles de vues. Mais, rarement artiste fut aussi énergiquement soutenu par ses pairs. Peintres, écrivains et hommes politiques s’engageront pour défendre cet homme délicieux, grand mondan et travailleur acharné. Considéré souvent comme un précurseur du mouvement impressionniste au sein duquel il comptait des amis, Renoir et Monet entre autres, il était surtout un peintre solitaire œuvrant pour la réalité dans l’intimité de son atelier. « M. Manet n’a prétendu ni renverser une ancienne peinture, ni en créer une nouvelle. Il a cherché simplement à être lui-même et non un autre », s’était-il plu à écrire dans le catalogue d’une exposition organisée à ses frais en marge du Salon de 1867. Novateur et libre de toute attache formelle à laquelle relier son œuvre, Manet est résolument le maître de l’art moderne.
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