Functioning in depression: a major challenge

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Major depressive disorder (MDD) is a disabling disorder with significant global, societal, and economic impact. It is concerning that the majority of MDD patients treated with antidepressants fail to achieve symptomatic remission, which adversely affects their quality of life and cognitive functioning. Furthermore, the alleviation of depression symptoms is not strongly correlated with functional improvement, which often occurs over a longer trajectory. In fact, some evidence suggests that functioning can be enhanced irrespective of change in depressive symptoms. From the patient’s perspective, a return to function (returning to usual levels of activity, feeling in emotional control, and enjoying relationships) is paramount to “feeling well,” and is a preferred priority over the absence of depressive symptoms. Furthermore, approximately 50% of MDD patients who meet symptom criteria for remission do not consider themselves to be in remission. This suggests that the overall burden of depression can be largely accounted for by loss of function as opposed to depressive symptoms. These factors have prompted a focus on function/quality of life during depression management, a trend that has resulted in regulatory bodies now encouraging the inclusion of functional outcome data in new drug submissions.

Diverse clinical profiles of MDD and functional status

Through public awareness and treatment advances, there has been a sizable shift in managing MDD from an inpatient model of care to a community-based outpatient approach, where more depressed patients are dealing with work-related issues. This coincides with an increased focus on depression in the workplace and functional outcomes. At the same time, the recurrent nature of depressive episodes draws comparisons to other chronic diseases such as rheumatoid arthritis or renal failure. The extent of impairment in functioning and well-being in MDD compared with other chronic conditions was first reported in the Medical Outcomes Study, in which greater social and physical impairment, poorer quality of life, more days in bed with

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by S. H. Kennedy and A. Cyriac, Canada

Maj or depressive disorder (MDD) is a disabling disorder with significant global, societal, and economic impact. It is concerning that the majority of MDD patients treated with antidepressants fail to achieve symptomatic remission, which adversely affects their quality of life and cognitive functioning. Furthermore, the alleviation of depression symptoms is not strongly correlated with functional improvement, which often occurs over a longer trajectory. In fact, some evidence suggests that functioning can be enhanced irrespective of change in depressive symptoms. From the patient’s perspective, a return to function (returning to usual levels of activity, feeling in emotional control, and enjoying relationships) is paramount to “feeling well,” and is a preferred priority over the absence of depressive symptoms. Furthermore, approximately 50% of MDD patients who meet symptom criteria for remission do not consider themselves to be in remission. This suggests that the overall burden of depression can be largely accounted for by loss of function as opposed to depressive symptoms. These factors have prompted a focus on function/quality of life during depression management, a trend that has resulted in regulatory bodies now encouraging the inclusion of functional outcome data in new drug submissions.

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Medicographia. 2014;36:435-440
www.medicographia.com

Selected abbreviations and acronyms

- MDD: major depressive disorder
- MDE: major depressive episode
- MRI: magnetic resonance imaging
- rTMS: transcranial magnetic stimulation
- SDS: Sheehan Disability Scale
fewer pain-free days, higher treatment costs, and a lower perception of health status was observed in depressed patients compared with those with diabetes, hypertension, coronary artery disease, arthritis, and back, lung, and gastrointestinal disorders. Not only is MDD a chronic, recurrent, and often treatment-refractory condition, but the disorder itself is frequently accompanied by other psychiatric (anxiety disorders, substance use disorders) and medical comorbidities (diabetes, overweight/obesity, cardiovascular disease). This can lead to further decrements in quality of life compared with non-comorbid MDD patients, as Das and colleagues demonstrated in a comparison of depressed patients with and without diabetes mellitus. Importantly, there appears to be a bidirectional relationship between depression and comorbidity, where one can exacerbate or trigger the other. Pharmacological treatment of depression in patients with comorbid medical conditions can improve clinical outcomes, but prescribers must pay particular attention to increased sensitivity to side effects and drug-drug interactions.

Strategies to enhance function

Impairment in neurocognition is increasingly recognized as a determinant of functional outcome in depression. Cognitive symptoms, including difficulty making decisions, loss of cognitive flexibility, and memory impairment are associated with limited functional recovery. Impairments in cognition (processing speed, attention, memory, and executive function) persist in remitted states. In one study where young depressed outpatients were followed for almost 2 years, neuropsychological test performance (executive function, memory, and attention) at baseline predicted 47.5% of the variability in functional outcome at end point.

Enhancing function in MDD can be achieved in several ways. For instance, some antidepressant treatments may be preferred over others in order to specifically treat neurocognitive impairments and functional deficits. Adjunctive treatments with psychostimulants may also be beneficial. A third option is to augment antidepressant therapy with nonpharmacological rehabilitation strategies such as cognitive remediation.

The aim of cognitive remediation therapy is to improve specific skills (processing speed, attention, memory, executive functions) through weekly training sessions using computerized drills, strategy monitoring, and application of skills to real-life settings. Although initial studies focused on schizophrenia, there is recent evidence to support the addition of cognitive remediation to medication in depressed patients, particularly with the aim of improving workplace function. Bowie and colleagues evaluated a form of cognitive remediation, which involved 15 hours of group treatment plus supplemental online computerized exercises in a small group of treatment-resistant depressed patients. There was a significantly greater improvement on attention/information processing speed and verbal memory in those receiving cognitive remediation compared with wait-list controls, with a trend toward improvement in real-world functioning. This represents a promising new approach which should be explored in larger patient samples of depressed patients.

The need for diagnostic refinement

While these interventions represent an incremental advance in dealing with functional impairment, a more fundamental issue relates to the diversity of clinical profiles in major depressive episodes (MDEs). It is hard to imagine that two patients, one with depressed mood, insomnia, weight loss, psychomotor agitation, and inappropriate guilt and the other with diminished pleasure, hypersomnia, weight gain, psychomotor retardation, and loss of energy, have similar abnormalities in underlying neural circuitry. This contrast illustrates the enormous number of clinical phenotypes that encompass a MDE diagnosis. Based on current DSM symptom criteria, there are almost 1500 potential combinations of symptoms that would satisfy diagnostic criteria for a MDE.

After decades of attempting to define depression subtypes purely on the basis of phenotypic expression (eg, melancholic, atypical, anxious), increased neuroimaging resolution and greater access to magnetic resonance imaging (MRI) and other scanning techniques now permit complex explorations of the brain at rest (default-mode network) or responding to emotional/cognitive challenges. Using these techniques, anhedonia has emerged as a potential endophenotype that may reflect differences in behavior and neural circuitry in a subgroup of individuals with MDD. This construct was described by John Haslam in 1809 as a “neglect [of] those objects and pursuits which formerly proved sources of delight and instruction.” Subsequently, the French Psychologist Théodule Ribot introduced the term “anhedonie.” However, it was the psychopharmacologist Donald Klein’s identification of anhedonia as an “unreactive pervasive impairment of the capacity to experience pleasure or respond affectively to the anticipation of pleasure” that contributed to its inclusion as a core symptom of a MDE in DSM-III (reviewed in reference 33).

There is evidence that low reward engagement is specific to depression compared with anxiety disorders or schizophrenia, and subsequent studies have also demonstrated that anhedonia is a unique predictor of antidepressant nonresponse which correlates with ventral striatal, and anterior cingulate activity. This marker of decreased or absent positive affect has also been evaluated in treatment studies showing differential effects of various antidepressants. For example, agomelatine differentially enhances interest and pleasure compared with venlafaxine, despite similar effects of both drugs on standard depressive symptoms. Anhedonia has also been identified as a moderator of response to repetitive transcranial magnetic stimulation (rTMS) in an evaluation of rTMS to the dorsomedial prefrontal cortex. In this trial, there was a bimodal separation of responders and nonresponders with clinical and...
IMRI profiles at baseline showing clear distinctions between the two groups. Poor response was associated with high connectivity between the dorsolateral prefrontal cortex and ventral striatum/ventral tegmentum/substantia nigra as well as hippocampus, a finding which was primarily observed in anhedonic patients. Importantly, anhedonia predicts poor prognosis with medical comorbidity. There is also evidence that social anhedonia, characterized by social skill impairments during social interactions and reduced emotional responsivity, limits an individual's willingness to engage in future social interactions. In summary, anhedonia represents a promising clinical and neuroimaging biomarker that deserves further investigation to assess interventions targeting social or occupational functioning in depressed patients.

Acknowledgment: The authors would like to express their gratitude to Sakina Rizvi for her input into the development of this manuscript.

References

Keywords: anhedonia; depression; functioning; major depressive disorder; major depressive episode; therapeutic efficiency
Le trouble dépressif majeur (TD M) est une affection invalidante dont l’impact global, sociétal et économique est significatif. Il est particulièrement préoccupant que la majorité des patients atteints de TD M traités par des antidépresseurs n’obtiennent pas de rémission symptomatique, ce qui affecte négativement leur qualité de vie et leur fonctionnement cognitif. En outre, le soulagement des symptômes dépressifs n’est pas fortement corrélé à une amélioration fonctionnelle, qui ne survient souvent qu’au long cours. En fait, d’après certaines données, le fonctionnement peut être amélioré indépendamment de l’évolution des symptômes dépressifs. Du point de vue du patient, une reprise du fonctionnement (retour au niveau habituel d’activité, sensation de contrôle émotionnel et satisfaction dans les relations) est essentielle pour « se sentir bien », et prioritaire sur l’absence de symptômes dépressifs. Environ 50 % des patients atteints de TD M répondant aux critères symptomatiques d’une rémission ne se considèrent pas eux-mêmes comme étant en rémission. Cela suggère que la charge globale de la dépression peut être en grande partie attribuée à une perte de fonctionnement, et non aux symptômes dépressifs. Une attention particulière a donc été portée au fonctionnement et à la qualité de vie lors de la prise en charge de la dépression, ce qui a conduit les organismes réglementaires à encourager désormais l’inclusion de critères d’évaluation fonctionnels dans les nouvelles demandes d’autorisation de mise sur le marché. L’échelle d’incapacité fonctionnelle de Sheehan (Sheehan Disability Scale, SDS) est de plus en plus souvent incluse comme critère d’évaluation dans les études cliniques conçues pour différencier les résultats symptomatiques et fonctionnels chez les patients suivant un traitement antidépresseur. Par conséquent, il y a eu une transition vers l’« efficacité thérapeutique » ce qui a entraîné l’intégration de l’efficacité et de la sécurité d’emploi clinique d’une part et de l’amélioration fonctionnelle d’autre part, ainsi qu’une prise en compte plus importante des critères économiques.

Différents profils cliniques du TDM et statut fonctionnel
La prise en charge du TDM, sous l’impulsion de la prise de conscience du public et des avancées thérapeutiques, est passée d’un modèle de soins par hospitalisation à une approche ambulatoire communautaire, un plus grand nombre de patients déprimés étant confrontés à des problèmes liés à l’emploi. Cela coïncide avec un intérêt plus particulièrement porté sur la dépression sur le lieu de travail et sur les critères d’évaluation fonctionnels. Parallèlement, de par leur nature récurrente, on peut comparer les épisodes dépressifs avec d’autres maladies chroniques, notamment la polyarthrite rhumatoïde ou l’insuffisance rénale. La Medical Outcomes Study a été la première étude comparant les altérations du fonctionnement et du bien-être dans le TDM à celles causées par d’autres affections chroniques : une altéra-
tion sociale et physique plus importante, une qualité de vie plus dégradée, un nombre de jours d’altération plus élevé avec moins de jours sans douleur, des coûts de traitement plus importants et une perception plus défavorable de leur état de santé ont été observés chez les patients déprimés par rapport à ceux atteints de diabète, d’hypertension, de coronaropathie, d’arthrose et de troubles dorsaux, pulmonaires et gastro-intestinaux. Le TDM est une affection chronique, récurrente et souvent réfractaire au traitement, qui est de plus fréquemment accompagné d’autres comorbidités psychiatriques (troubles anxieux, troubles liés aux substances) et médicales (diabète, surpoids/obésité, maladies cardio-vasculaires) susceptibles de dégrader encore davantage la qualité de vie par rapport à des patients atteints de TDM sans comorbidité, comme l’ont démontré Das et al. en comparant des patients déprimés atteints ou non de diabète sucré. Il est important de souligner qu’il semble exister une relation bidirectionnelle entre la dépression et la comorbidité, l’une pouvant exacerber ou déclencher l’autre. Traiter pharmacologiquement la dépression chez les patients présentant des comorbidités médicales permet d’améliorer les résultats cliniques, mais les prescripteurs doivent être particulièrement attentifs à l’aggravation d’une sensibilité aux effets indésirables et aux interactions médicamenteuses.

**Stratégies permettant d’améliorer le fonctionnement**

L’altération de la neurocognition est de plus en plus souvent considérée comme un élément déterminant de l’évolution fonctionnelle dans la dépression. Les symptômes cognitifs, notamment la difficulté à prendre des décisions, la perte de la flexibilité cognitive et l’altération de la mémoire, sont associés à une limitation de la récupération fonctionnelle. Des déficits cognitifs (rapacité de traitement de l’information, attention, mémoire et fonction exécutive) persistent dans les états de rémission. Dans une étude suivant de jeunes patients déprimés pendant près de deux ans, les résultats des tests neuropsychologiques (fonctions exécutives, mémoire et attention) au début de l’étude ont permis de prévoir 47,5 % de la variabilité de l’évolution fonctionnelle à la fin de celle-ci.

L’amélioration du fonctionnement dans le TDM peut être obtenue de différentes manières. Par exemple, certains traitements antidépresseurs peuvent être privilégiés par rapport à d’autres afin de traiter plus spécifiquement les troubles neuropsychologiques et les déficits fonctionnels. Des traitements complémentaires par des psychostimulants peuvent également être bénéfiques. Une troisième option est d’optimiser le traitement antidépresseur avec des stratégies de rééducation non pharmacologique, par exemple la remédiation cognitive.

**Nécessité d’un affinement du diagnostic**

Ces traitements constituent une avancée dans la prise en charge de l’altération fonctionnelle, mais la diversité des profils cliniques dans les épisodes dépressifs majeurs (EDM) pose un problème plus fondamental. Il est difficile d’imaginer que deux patients, l’un d’humeur dépressive, présentant des somnolences, une perte de poids, une agitation psychomotrice et une culpabilité inadaptée et l’autre une diminution du plaisir, une hypersomnie, un gain de poids, un retard psychomoteur et une perte d’énergie, présentent des anomalies similaires des circuits neuronaux sous-jacents. Ce contraste illustre le nombre considérable de phénotypes cliniques que recouvre un diagnostic d’EDM. Selon les critères symptomatiques de la version actuelle du DSM, il existe près de 1 500 combinaisons potentielles qui pourraient répondre aux critères diagnostiques d’un EDM.

Après avoir, pendant des décennies, tenté de définir des sous-types de dépression exclusivement sur la base de l’expression phénométique (par exemple, mélancolique, atypique, anxiéux), l’amélioration de la résolution de la neuro-imagerie et un accès plus facile à l’imagerie par résonance magnétique (IRM) et aux autres techniques d’imagerie permettent désormais des explorations complexes du cerveau au repos (réseau cérébral par défaut) ou des réponses à des provocations émotionnelles et cognitives. Grâce à ces techniques, l’anhedonie apparaît comme un endophénotype potentiel pouvant refléter des différences plus subtiles de la dépression.
férences de comportement et de circuits neuronaux dans un sous-groupe de patients atteints de TDM. Cette entité a été décrite par John Haslam en 1809 comme un comportement tendant à « négliger les objets et les activités qui constituaient auparavant des sources de plaisir et d’instruction ». Par la suite, Théodule Ribot, un psychologue français, a introduit le terme d’« anhédonie ». Cependant, c’est le psychopharmacologue Donald Klein qui a identifié l’anhédonie comme « une altération généralisée non réactive de la capacité de ressentir du plaisir ou de répondre de manière affective à l’anticipation d’un plaisir » et a contribué à l’inclure comme symptôme principal d’un EDM dans le DSM-III (examiné dans la référence 33).

D’après certaines données, une faible participation au processus de récompense est spécifique de la dépression par rapport au trouble anxieux ou à la schizophrénie, et dans des études ultérieures l’anhédonie s’est aussi établie comme un facteur de prédiction unique de non-réponse aux antidépresseurs. Ce marqueur de la diminution ou de l’absence d’affect positif a également été évalué dans des études thérapeutiques montrant les différents effets de plusieurs antidépresseurs. Par exemple, l’agomélatine augmente de manière différentielle l’intérêt et le plaisir par rapport à la venlafaxine, malgré les effets similaires des deux médicaments sur les symptômes dépressifs standard. L’anhédonie a également été identifiée comme un modérateur de réponse à la stimulation magnétique transcrânienne répétée (SMTr) dans une évaluation de la SMTr sur le cortex préfrontal dorsomédian. Dans cette étude, une séparation bimodale a été observée entre les répondeurs et les non-répondeurs dont les profils entre les deux groupes, définis par la clinique et l’imagerie par résonance magnétique fonctionnelle (IRMf), différaient clairement à l’inclusion. Une mauvaise réponse est associée à une connectivité élevée entre le cortex préfrontal dorsolatéral et le corps strié ventral/le tegmentum ventral/le locus niger, ainsi que l’hippocampe, un résultat principalement observé chez les patients anhédoniques. Il est important de souligner que l’anhédonie constitue un facteur de prédiction d’un mauvais pronostic en présence de comorbidités médicales. Il a également été montré que l’anhédonie sociale, caractérisée par une altération des capacités sociales au cours d’interactions sociales et une réduction de la réponse émotionnelle, limite la volonté individuelle de participer à des interactions sociales ultérieures.

En résumé, l’anhédonie est un biomarqueur clinique et de neuro-imagerie prometteur, justifiant des recherches complémentaires afin d’évaluer les actions ciblant le fonctionnement social ou professionnel chez les patients déprimés.

**Mots clés :** anhédonie ; dépression ; épisode dépressif majeur ; efficacité thérapeutique ; fonctionnement ; trouble dépressif majeur

**Remerciements :** Les auteurs souhaitent exprimer leur gratitude à Sakina Rizvi pour sa contribution à la rédaction de ce manuscrit.
The DSM-5 criteria for a major depressive episode comprise two symptoms that represent impaired affect modulation: depressed mood and anhedonia, including lack of pleasure, and both are considered as core symptoms (Table I, page 442). The criteria further comprises two somatic symptoms (appetite, sleep), two cognitive symptoms (concentration, guilt/worthlessness), an affective-cognitive-somatic symptom (fatigue/loss of energy), a behavioral symptom (retardation or agitation), and a suicidality symptom. The emotion-based understanding of depression focuses on impaired affect modulation: an excess of negative affect (depressed mood) and a lack of positive affect (decreased pleasure in most activities). Impaired affect modulation in depression could also be seen as increased activation and/or duration of negative affect (sadness/irritability) or diminished activation and/or duration of positive affect. Some authors investigated the presence of positive and negative affect as two separate dimensions, while others investigated the ratio of positive over negative affect. Although there is ongoing discussion regarding whether antidepressants with different mechanisms of action target different aspects of depression, it has been suggested that serotonergic and serotonergic/noradrenergic agents have a stronger effect on guilt, fear, irritability, and anxiety, while noradrenergic and dopaminergic agents have a stronger effect on loss of pleasure and enjoyment, loss of motivation and energy and loss of interest.

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Affect modulation, functioning, and depression

by K. Demyttenaere, Belgium

The DSM-5 criteria for a major depressive episode comprise two symptoms that represent impaired affect modulation (depressed mood and anhedonia) and require “a clinically significant distress or impairment in social, occupational, or other important areas of functioning.” The latter is often not taken into account but could be helpful in diagnosing and identifying “really” depressed patients. When looking at outcomes, standard scales mainly focus on changes in symptom severity, while changes in positive affect and changes in functioning or quality of life are poorly represented. Looking beyond symptoms could help clinicians in better assessing differences between different (classes of) antidepressants, and it has been shown that functioning predicts remission as well as relapse and recurrence independently from symptom severity. The relation between symptoms (including affect modulation) and functional recovery has been insufficiently investigated and mediating factors such as cognition or feelings of embarrassment (stigma) could play an important role. It has been shown that absenteeism (as a measure of occupational impairment) decreases during treatment with antidepressants but one should avoid violated expectations: in community samples, untreated depressed patients perform better than treated depressed patients, again suggesting that mediating variables should be taken into account.

Medicographia. 2014;36:441-445 (see French abstract on page 445)
negative affect (resulting in a positivity index), while still others investigated these affects in a more dynamic way by looking at the time courses of both affects (eg, how much time is needed to experience positive affect after an increase in negative affect?). It has also been postulated that depression stems not only from inadequate engagement in pleasurable activity and excessive experience of aversive events, but also from the diminished reward value of potentially pleasant events and the heightened averseness of unpleasant events (Table II).

But positive affect and positive emotions can be divided in several subgroups. A first subgroup is achievement-based (the drive and/or pleasure of achieving): “energetic,” “lively,” “active.” A second subgroup of emotions is affiliative-based (safety): “feeling safe,” “feeling secure,” “warm.” And a third subgroup relates to well-being (soothing and calming): “contentment,” “peacefulness,” “relaxed,” “peaceful.” There is a link between positive affect and approach behavior and goal-directed behavior: it has actually been postulated that the expectation of reward (positive affect) engenders approach motivation and facilitates goal-directed behavior toward rewarding stimuli (achievement-based or affiliative-based) and that there hence is a link between sensitivity to signals of incentive reward and positive emotionality. Achievement-based or affiliative-based behavior has, by definition, a link with functioning.

The DSM definition also requires “a clinically significant distress or impairment in social, occupational, or other important areas of functioning.” This criterion was included to minimize false positive diagnoses, although its usefulness is debatable: many of these symptoms (decreased interest, concentration problems, fatigue or loss of energy, psychomotor retardation, or agitation) inherently result in significant functional impairment; this clinical significance criterion could therefore be at risk of being redundant or of creating false negative diagnoses. An example of this possible contradiction is a study in a primary care patient population fulfilling the DSM symptom criteria for major depression, where 28% of the patients did not have clinically significant impairment—defined as at least moderate impairment (a score of ≥4) in the three domains (occupational, social, and family functioning) of the Sheehan Disability Scale (SDS). About two-thirds of these outpatients had impairment scores between 5 and 8 (≥4 is mild impairment, ≥7 is severe impairment).

**Measuring outcomes in antidepressant treatment: beyond symptom scales**

It is difficult to demonstrate clinically relevant differences in efficacy between different antidepressants, perhaps because of the heterogeneity of patients with major depression but perhaps, also, because outcome measures are most often limited to observer-rated scales that focus only on symptoms. Self-rated scales or changes in positive affect, mobility, or quality of life are most often not assessed, and if they are assessed they are most often poorly reported in the literature. It is remarkable that anhedonia (lack of interest and pleasure

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<td>1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observation made by others (eg, appears tearful).</td>
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<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).</td>
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<td>3. Significant weight loss when not dieting or weight gain (eg, change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.</td>
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<td>4. Insomnia or hypersomnia nearly every day.</td>
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<td>5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).</td>
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<td>6. Fatigue or loss of energy nearly every day.</td>
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<td>7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).</td>
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<td>8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).</td>
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<td>9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.</td>
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<th>Table II. Affect dysregulation in depression: increased activation and/or duration of negative affect (sadness/irritability) or diminished activation and/or duration of positive affect and motivation. After reference 6. Demiryüzen et al. Annu Rev Clin Psychol. 2011;7:1-38. © 2011, Annual Reviews.</th>
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<td>1. A lower threshold to activate negative affect</td>
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<td>2. A more intense response once negative affect is activated</td>
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<td>3. Difficulty terminating a negative affect response</td>
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<td>4. Activation of negative affect in inappropriate contexts</td>
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<td>5. Cognitive distortion or excess attention directed to a typical internal negative affect response</td>
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<td>6. Elevated threshold to activate positive affect</td>
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<td>7. A less intense response once positive affect is activated</td>
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<td>8. Difficulty sustaining a positive affect response</td>
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<td>9. Failure to activate positive affect in appropriate contexts</td>
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Insufficient devotion of cognitive resources to initiating, sustaining, or enhancing a typical internal positive affect response.
in most activities)—despite being considered as a core diagnostic criterion—is only poorly represented in the most frequently used outcome scales (the HAMilton Depression rating scale [HAM-D] and Montgomery-Asberg Depression Rating Scale [MADRS]).

Despite the acceptance of functioning as an important diagnostic and outcome criterion, many randomized clinical trials actually do not report functional outcomes: in a systematic review of 203 depression trials (77% drug therapy studies and 23% psychotherapy studies) functional outcome scales were used in fewer than 5% of trials. Moreover, it has been shown that the correlation between symptom scales and functioning scales is only moderately high, which suggests that they are largely independent dimensions that may need different treatment approaches.

However, several findings support the use of outcome measures that go beyond symptom scales.

First, this approach could help the clinician to make a better assessment of the differences between different antidepressants. Indeed, 52.3% of psychiatrists take the presence of a specific symptom or symptom profile into account for prescribing a specific antidepressant. And although there is ongoing discussion regarding whether antidepressants with different mechanisms of action target different aspects of depression, it has been suggested that serotonergic and serotonergic/noradrenergic agents have a stronger effect on guilt, fear, irritability, and anxiety, while noradrenergic and dopaminergic agents have a stronger effect on loss of pleasure and enjoyment, loss of motivation and energy, and loss of interest.

For example, patients treated with the noradrenergic agent reboxetine were shown to be more socially adjusted than patients treated with fluoxetine: the reboxetine–fluoxetine comparison showed a significant association with reboxetine for several items, while the opposite—ie significant association with fluoxetine—was not seen. The largest difference was found in six items: community involvement, interest in hobbies, social compliance, rejection sensitivity, control of surroundings, and vainness. Among these items, community involvement and social compliance explore active social behavior, while most of the others—ie, rejection sensitivity, control of surroundings, and vainness—investigate self-perception aspects. A 24-week comparative trial between escitalopram and duloxetine did not show significant differences in MADRS scores and rates of response and remission at end point; however, escitalopram showed a significant advantage over duloxetine for both total SDS score and occupational impairment score. A study comparing agomelatine and venlafaxine did not show any significant difference in HAM-D score, but agomelatine did significantly better than venlafaxine in improving hedonic function. Although it could be hypothesized that an increase in positive affect is more important than a decrease in negative affect for restoring functioning, more data are still needed to provide a final answer to this question.

Second, going beyond symptom scales scores could help in predicting remission. In a 6-month follow-up study of 1083 patients with a mood disorder that used a multiple regression model for clinical remission six months after enrollment, age, race, and gender were not found to be significant predictors of remission; however, being married was (odds ratio [OR], 1.323; confidence interval [CI], 1.013-1.727; P=0.040) and patients with severe baseline functional impairment (the “extremely difficult” category) had a significantly lower chance of remission (OR, 0.610; CI, 0.392-0.945; P=0.028) at six months compared with patients with mild baseline functional impairment (the “somewhat difficult” group) even when controlled for baseline depression severity, anxiety level, and alcohol use. Similarly, another naturalistic study with 1359 patients showed that baseline occupational status (again in a multivariate analysis) was a highly significant predictor of symptomatic outcome 6 months later (using “unemployed” versus “working for pay” as reference category: OR, 0.52 (CI, 0.35-0.75; P=0.001).

Third, going beyond symptom scales scores could help in predicting relapse and recurrence. During a two-year maintenance treatment with citalopram, discriminant analysis correctly predicted the presence or absence of recurrence in 84.38% of subjects, suggesting that functional recovery is a powerful predictor of long-term outcome, even in patients with symptomatic remission. In a trial of cognitive-behavior therapy where patients were followed-up for 24 months, psychosocial dysfunction level predicted monthly changes in depressive symptoms and relapse (but depressive symptom severity did not predict functioning); deteriorations in psychosocial functioning may signal imminent major depressive relapse/recurrence and provide targets for change during treatments focused on relapse/recurrence prevention.

Fourth, more data on functioning in patients with depression would result in a better understanding of the relation between symptomatic and functional recovery. In fact, multiple questions on this relation remain incompletely answered. A naturalistic study investigated the relation between symptomatic and functional remission in more detail by following patients with complete or partial remission for 6 months. Symptomatic improvement was assessed with the HAMD scale and improvement in functioning with the Social and Occupation-

**Selected Abbreviations and Acronyms**

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
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<tr>
<td>MDE</td>
<td>major depressive episode</td>
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<tr>
<td>SDS</td>
<td>Sheehan Disability Scale</td>
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<tr>
<td>SOFAS</td>
<td>Social and Occupational Functioning Assessment Scale</td>
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al Functioning Assessment Scale (SOFAS), with normal functioning being defined as a score ≥80. Again, the time course of symptomatic and functional improvement were comparable, hence challenging the idea that functional improvement lags behind symptomatic improvement. A high correlation was reported between the SOFAS and HAMD-17 scales throughout the study (Pearson correlations at baseline, 0.62, P<0.0001; at end point, 0.63, P<0.0001), which means that improvements in symptom severity and functional impairment from depression are significantly correlated.

The HAMD score for complete remitters (HAMD ≤7) was 4.3 at baseline and 4.0 after six months of follow up, and for partial remitters the HAMD-D score was 12.0 and 7.2 respectively; the SOFAS score for complete remitters was 80.4 at baseline and 84.6 at six-month follow-up, and for partial remitters the SOFAS score was 62.8 and 76.2, respectively. But these results also show that even in symptomatically remitted patients, functioning is still suboptimal even 6 months later (23% patients still not reaching normal functioning). Twenty-four percent of patients with a HAMD-17 score of ≤7 did not have normal levels of functioning at the end of the six-month follow-up period, and even when using a cutoff score of ≤5, 17% of the patients still had functional impairment. By plotting receiver operating characteristics (ROC) curves, the authors showed that a score of ≤5 on the HAMD scale maximized both sensitivity and specificity for identifying normal levels of functionality with respect to other scores, suggesting that the more frequently used score of ≤7 is too high.24 At baseline, partial remitters had lost 44 working days in the past 3 months (start of treatment) and at end point they had lost 63 days in the past 6 months (a decrease in work loss of about 30%). For complete remitters, this was 21 and 20 days, respectively (a decrease in work loss of about 50%). A review on the relations between depression and functioning (social, occupational, and physical) showed that these domains related moderately well with measures of depressive symptoms but not so well as to be seen as redundant: the authors concluded that the relationship between symptoms and functioning is complicated, and that functioning tends to be less responsive to treatment.26

Other studies have also showed that treatment of depression actually results in a dramatic decrease in absenteeism: the mean number of work days lost was 11.0 in the 3 months before initiation and 5.4 days in the 3 months following initiation of antidepressant treatment: the effect was largest for absences of 6 consecutive days of more.28 But one should stay cautious when trying to draw conclusions from depressed subjects seeking help and being treated as they may differ from those not seeking help (in the general population). In fact, a large epidemiological study has showed that 56% of depressed patients on treatment claimed to be "working as carefully as usual in the past 4 weeks" whereas for those not on treatment, the percentage was 66%; similarly, 45% of depressed patients on treatment said that they had "accomplished as much as usual in the past 4 weeks" while the figures was 56% for those not receiving treatment.27 A more recent replication of this study found similar results for ICD-10–confirmed depression, anxiety disorders, and schizophrenia: compared with not receiving treatment, receiving treatment was consistently associated with nonparticipation in the labor force (part-time employment, looking for work, or not being in the labor force), and was negatively associated with work performance (working as carefully as usual in the past 4 weeks and accomplishing as much as usual in the past 4 weeks).28 The latter studies illustrate the fact that depressed patients on treatment and those not on treatment differ not only in their help-seeking behavior, but probably also in their personality characteristics and psychosocial context.

A large European study focused on factors mediating the relation between depression and functioning and a path analysis found that approximately half of the impact of MDE on role functioning was not mediated by depression directly, but indirectly by problems with cognition (measured with five items that included questions about difficulties with concentration, memory, understanding, and ability to think clearly) and by feelings of embarrassment (measured with one item: "how much embarrassment did you experience because of your health problems during the past 30 days?").29 Therefore, more specific interventions aimed at improving these mediating factors could be helpful in improving the societal effects of MDE on role functioning. Focusing on concentration and attention may lead to improved role functioning. Embarrassment is related to a negative evaluation of oneself and limits the ability to engage in effective social interaction. Patients with MDE are at risk of being embarrassed about their condition because of self-stigmatization. Moreover, it has been shown that stigma in MDE patients is associated with greater unmet mental health care needs and with antidepressant drug noncompliance.30,31

In conclusion, although the DSM criteria for major depression clearly comprise affect modulation items (depressed mood as well as loss of pleasure) and include a functional impairment criterion, the most frequently used observer rating scales used to assess change during treatment do not sufficiently cover changes in positive affect and changes in functioning, even though assessing these changes could help clinicians in better understanding the differences in efficacy between different (classes of) antidepressants. Moreover, functional impairment seems to be a predictor of remission, relapse, and recurrence even after controlling for symptom severity.

Keywords: agomelatine; depression; functioning; negative affect; positive affect
MOOD MODULATION, FUNCTIONING, AND DEPRESSION

Deux symptômes des critères du DSM-5 pour un épisode dépressif majeur représentent la dégradation de la modulation de l’affect (humeur dépressive et anhedonie) ; ces critères nécessitent « une souffrance cliniquement significative ou une altération du fonctionnement social, professionnel ou dans d’autres domaines importants ». Ce dernier est souvent omis mais pourrait aider au diagnostic et à l’identification des patients « vraiment » déprimés. Si l’on considère les résultats, les échelles standard s’intéressent principalement aux modifications de la sévérité des symptômes aux dépens des modifications des affects positifs et du fonctionnement ou de la qualité de vie, peu représentés. Les médecins évalueront mieux les différences entre les classes d’antidépresseurs en regardant au-delà des symptômes et le fonctionnement est un facteur prédictif de la rémission, de la rechute et de la récidive, indépendant de la sévérité du symptôme. La relation entre les symptômes (y compris la modulation de l’affect) et la guérison fonctionnelle n’a pas été assez analysée et les facteurs de médiation comme la cognition ou les sentiments de gêne (stigma) pourraient jouer un rôle important. L’absentéisme, en tant que mesure d’altération du fonctionnement professionnel, diminue pendant le traitement antidépresseur mais il faut éviter les attentes trompeuses : dans des échantillons collectifs, les patients déprimés non traités réussissent mieux que des patients déprimés traités, ce qui montre encore que les variables médiatrices devraient être mieux prises en compte.
Hot cognition is the most obviously disturbed and disturbing domain of psychological function for the depressed patient. The primary symptoms of depressed mood are markedly diminished interest or pleasure, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicidal ideation. They all represent the powerful emotional content that shapes the experience and presentation of major depression.

Cognition is usually defined as the mental process whereby knowledge and understanding is acquired through thought, experience, and the sense organs. The use of the word in psychology has extended to include active processes such as judging and problem solving, imagination, and even planning. Accordingly, it has come to encompass, by such extension, essentially emotional components of experience because choice and decision-making are inherently based on the values that form the basis of our emotional life. It nevertheless remains convenient to

It is convenient to distinguish the cognition associated with the emotions, sometimes called hot cognition, from the cold cognition that is associated with simple acts of remembering, calculating, planning, or executing complicated but essentially emotion-free tasks. While it is unsurprising that hot cognition is distorted by extreme mood states like major depression and mania, it would not necessarily follow that cold cognition be also affected. In fact, the centrality of impaired cold cognition has now been empirically established for major depression, together with the related problem of psychomotor slowing. Nevertheless, actual measurement using standard methods from neuropsychology is not a standard of care in psychiatry. It probably should be, because persisting symptoms of impaired episodic memory and reduced motivation are probably linked to the subjective experience of anhedonia. Moreover, they limit the capacity for full functional recovery from major depression. Experimental studies in animals and man suggest that the cognitive impairments of depression are at least partially reversible by antidepressants. This implies that improved outcomes in major depression may be achievable by targeting cognition rather than just depressive symptoms. Hot cognition has been the obvious focus for understanding mood disorder, and cognitive behavior therapy was developed as a specific remedy for the extreme negative cognitive distortions of the depressed state. Its efficacy is usually taken to be a reasonable proof that the cognitive mechanisms it targets are actually a fundamental part of the illness. It poses a secondary question, which is how antidepressants might work on essentially the same processes. This can now be studied more easily because neuroscience has taught us that there is a bridge between hot and cold cognition via studies of motivation and reward. This is encouraging a more subtle approach to distinguishing different components of emotion, particularly anhedonia, and the contribution of pleasure to full functional recovery from depression.
distinguish the cognition associated with the emotions, sometimes called hot cognition, from the cold cognition that is associated with simple acts of remembering, calculating, planning, or executing complicated but essentially emotion-free tasks. Like all such distinctions, the hot/cold dichotomy is valid for the extreme examples of the two kinds of cognition but breaks down when one approaches more nuanced mental processes.

Cold cognition is usually taken to include attention, memory, and executive function. These are all nouns that have ordinary language meanings and we can all give subjective accounts of how we believe our attention, memory, or executive function to be at any given moment. Accordingly, psychologists and psychiatrists sometimes use entirely subjective scales to decide whether or not individuals have impaired cognition of this kind. Subjective complaints about memory, for example, may precede the onset of frank dementia but they are also clearly a part of major depression. Indeed, if one observes the criteria for a major depressive episode in DSM-5, shown in Table I, the 8th is “reduced concentration with diminished ability to think or concentrate, or indecisiveness.” So this kind of cognitive impairment is incorporated in the simplest definitions of a major depressive episode. Indeed, the cognitive impairment that it implies is frequently the reason why people may seek the attention of a doctor. Their inability to conduct daily activities that rely on simple memory, concentration, and decision-making may even define the severity of the depressed state and the requirement for treatment or, in the worse case, admission to hospital. Admission to hospital may often be required because of the complete failure of a patient’s executive capacity. Clearly, recovery of cold cognition is a necessity for recovery of everyday function.

Despite the centrality of impaired cognition and the related problem of psychomotor slowing in the presentation of depressed patients, actual measurement using standard methods from neuropsychology is not a standard of care in psychiatry for recovery of everyday function.

Measuring cold cognition

◆ Attention

Sustained attention is the ability to remain on target during boring repetitive tasks. It involves keeping in mind perceptions and instructions that allow relatively simple online decisions to be made. For example, if one is read out a sequence of numbers, one can determine how many numbers can be remembered in a sequence, either forwards or backwards. This so-called “digit span” test is a useful but rough-and-ready measure of attention. A somewhat more credible measure is from continuous performance tasks where the individual is required to view a screen with a sequence of symbols or numbers and the instruction is to identify when, for example, a particular sequence of numbers occurs. This can be programmed so the targets are relatively infrequent and the numbers change rapidly, which makes the task more difficult. Such tasks are subjectively effortful and there may be an interesting association with the effort of producing maximal handgrips for example, because similar central processes may be involved.

◆ Episodic memory

Episodic memory is usually measured using lists of nouns (typically 16), which are repeated on 5 occasions after each of which the subject is tested for immediate recall. Over the 5 tests the number recalled increases and the performance can also be evaluated after a delay, with intervening distraction. This test gives some idea of the rate at which learning occurs, the learning capacity (in other words the maximum number of words that can be remembered by an individual), and consolidation/recall.

◆ Executive function

Executive function is the term used to describe a host of different kinds of actions that have in common the prioritization and selection between different alternatives. In its simplest

<table>
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<th>Table I. Symptoms of a major depressive episode.</th>
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1. Depressed mood
2. Markedly diminished interest or pleasure
3. Significant weight loss
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, suicidal ideation, etc

Selected abbreviations and acronyms

- 5-HT: 5-hydroxytryptamine
- CBT: cognitive behavior therapy
- ECT: electroconvulsive therapy
- HAM-D: Hamilton Rating Scale for Depression
- SHAPS: Snaith-Hamilton Pleasure Scale
- SSRI: serotonin reuptake inhibitor
- TD: tryptophan depletion
- TMT: Trail Making Test

Impact of cognitive symptoms and anhedonia on functioning in depression – Goodwin
form this ability to switch set can go wrong, as an inability to learn that a particular contingency has changed. So if in a task that chooses between two different buttons, one button is the correct one in the first part of the test and is rewarded but the second button becomes the correct button after a finite period of time and without warning, then normally an adaptive response, when reward is withheld from button 1, is to try the other button and to discover that it is now the correct one. If this change of set fails to occur quickly, it is described as perseveration. Perseverative behavior is very characteristic of patients with major frontal lobe lesions and more subtle disturbances of executive function are often assumed to reflect abnormalities of frontal lobe function, or perhaps more correctly the functional networks that are routed through the frontal cortex.\textsuperscript{3}

**Disturbances of cold cognition in major depression**

All domains of cognitive function have been described as abnormal in major depression, particularly when patients are acutely depressed.\textsuperscript{1,5} The pattern of deficits is similar in younger and older groups, although memory and learning are more affected in those over 60.\textsuperscript{6} In the past, this was often discounted on the basis that patients were not trying, or were simply poorly motivated to cooperate with the experimental procedure. However, there is little evidence to suggest that this is actually the case, so for over a decade now the general consensus has been that the measured abnormalities in neuropsychological function should be accepted as genuine measures of the patient's ability to perform tasks.\textsuperscript{1} Moreover, failure on these tasks has important implications for real life functioning that will limit recovery and rehabilitation. There is, therefore, every reason to focus in the future on cold cognition in the design of treatment and management for patients with major depression.

The degree of memory impairment correlates modestly with the severity of depression measured on scales of largely subjective reports like the Hamilton Rating Scale for Depression (or HAM-D) and show a diurnal swing in the course of a day.\textsuperscript{4} This implies that the underlying neurobiology is linked to depression per se and that it may be quite quickly improved as mood improves. Meta-analysis has illustrated the magnitude and relative consistency of the effects. It confirms that formal tests should concentrate on attention, and particularly, memory.

The disturbance of memory function broadly recovers with treatment, even for example when the treatment is electroconvulsive therapy (ECT), but there have been relatively few clinical trials in which cognition has been measured as a potential treatment target for antidepressants. One unusual example found that a measure of speed/executive function improves significantly during treatment with duloxetine or the new antidepressant vortioxetine in elderly patients.\textsuperscript{7} It is not established what the best cognitive treatment target would be in major depression but one clue is the persistence of memory impairment following recovery from acute episodes. This has been looked at in a large general practice sample that suggested that the extent of impairment between episodes was related to the number of previous episodes the patient had suffered.\textsuperscript{8} This is compatible with the hypothesis that repeated episodes of depression are, in some sense, neurotoxic and result in accumulating impairments of cognition, which again may contribute to the difficulties such patients face in returning to work and the attainment of premorbid levels of function. The persistence of cognitive impairments in euthymic patients is nevertheless most striking in older patients and is seen across different domains relatively unselectively.\textsuperscript{9}

In depression, executive function is obviously disturbed because of the inability of the subject's experience in conducting the business of daily life. In terms of symptoms, as shown previously in Table 1, indecisiveness is a key part of item 8. It has two elements, one is a slowing and the other is a failed capacity to make decisions at all. These failures can be captured in the laboratory in a relatively straightforward way by tests that require simple alternation between different targets.

The simplest is the Trail Making Test (TMT), which requires subjects to join the dots between letters or words. Part A of the TMT simply determines speed (and comprehension of the test): it requires following either numbers or letters. The second part requires alternation between the sequence of letters and numbers; it is just about the simplest test of executive function one could devise and its primary output is the speed at which the task is completed.\textsuperscript{3} However, it would be possible to capture errors where subjects fail to actually make the necessary switch and, for example, continue to join letters rather than alternating to numbers. In depression, the dysfunction is primarily expressed as slowing in both phases of the TMT. Thus, in practice, measures of executive function in depression usually rely on an estimate of the speed to complete relatively simple executive tasks.

Another test that does this quite effectively and has been used in clinical trials in depression is the digit symbol substitution test, which requires subjects to copy a list of 9 symbols that have to be matched with corresponding numerical digits in a random sequence.\textsuperscript{3} The time taken to complete a fixed number of images or the number of images completed within a fixed time gives the measure. Tests of executive function are usually related to measures of intelligence simply because measures of intelligence are aggregated average measures of tests of executive function. It is therefore often useful to have an independent language-based measure of premorbid intelligence in patients with depression. The National Adult Reading Test is available in English (and other languages) to provide this estimate.\textsuperscript{10} It relies on the correct pronunciation of irregular words and correlates again with levels of education.
The pharmacology of cognitive impairment in depression

Most of the existing studies that have direct relevance to the use of antidepressants in general, and the selective serotonin reuptake inhibitors (SSRIs) in particular, relate to the role of serotonin in cold cognition. In man, tryptophan depletion has been taken to be one way of modestly reducing serotonergic function in the brain\(^1\): different loading doses of competing amino acids can produce different degrees of tryptophan depletion (TD). Across a wide range of studies the most consistent effects of tryptophan depletion was impairment of episodic memory, particularly that requiring verbal learning.\(^12\) This effect did not seem to extend to spatial memory or semantic or working memory or, indeed, executive function and sustained attention. These effects on memory may be more striking in individuals with a previous history of depression.\(^13\) It is notable that the effects of low level TD are obtained largely independently of effects on mood per se. Frank mood effects require high level TD and were first described in recovered patients receiving SSRI treatment.\(^14\) Comparable effects are also seen in recovered patients not on treatment,\(^15\) but are only seen in healthy volunteers if they have a family history of mood disorder.\(^16\) In fact, in vulnerable subjects there is an impact both on cold cognition (memory) and hot cognition (shown by negative cognitive bias but not frank depressive symptoms in patients at risk of depression).\(^17\)

The findings using drugs that putatively increase serotonin availability have been mixed. Thus, for example, following acute infusion of citalopram an effect on memory consolidation was found in healthy women, which, in part at least, compliments the corresponding findings from tryptophan depletion.\(^18\) Other studies have found a variety of other effects, often of impairment, which are difficult to interpret. There is a much more extensive and evolving data set in animals, which is beyond the scope of this article. Generally, it appears that effects of 5-hydroxytryptamine (5-HT) receptor subtype manipulation on learning and memory are exerted through alterations in the release of neurotransmitters such as acetylcholine and glutamate, which have been more directly implicated in cognitive function than 5-HT itself.\(^19\) It suggests the potential for modulation of attention and learning by a range of transmitter systems.

Hot cognition

Hot cognition is the most obviously disturbed and disturbing domain of psychological function for the depressed patient. The primary symptoms of depressed mood are markedly diminished interest or pleasure, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicidal ideation. They all represent the powerful emotional content that shapes the experience and presentation of major depression. In addition, the patients may describe these experiences as literally painful, and pain may indeed be the primary complaint of patients who present with depression. Hot cognition may be a literal barrier to normal personal and social function.

Cognitive behavior therapy

The hot cognitions that are so obvious in conscious experience have given rise to at least one very useful way of thinking about the experience of patients with depression. Half a century ago Aaron Beck identified negative thinking as a central feature of all states of depression.\(^19\) Such thinking focuses on oneself, the world, and the future. This triad in which suicidal ideation is particularly important struck him as an important maintaining factor in all types of depression. This conscious negativity provides the focus of cognitive behavior therapy. Cognitive behavior therapy takes what is essentially a Socratic approach to the patients’ experience and explores whether their beliefs and convictions about the world itself and the future are actually proportionate. The role of the therapist is to change the perceptions and experiences of the patient by reasoning. In doing so, therapists elicit the extremes of conscious emotional experience described by patients and become involved with the patients in ways that are hard to measure. The essential ingredients of cognitive behavior therapy (CBT) are therefore often confounded by nonspecific factors. For this reason, psychotherapy research faces considerable challenges in its choice of fair comparison treatments, but a relatively large literature supports its efficacy in major depression.\(^20\)

The efficacy of CBT is usually taken to be a reasonable proof that the cognitive mechanisms it targets are actually a fundamental part of the illness. It poses a secondary question, which is how antidepressants might work on essentially the same processes. It turns out that they also reverse cognitive biases, but of course not simply at a conscious level. Instead, measures of automatic emotional bias relating to the perception of the emotional content of faces or the memory for positive and negative material is both biased in a negative way in patients and reversed in a relatively short term by antidepressants.\(^21\) This convergence of antidepressant effects and CBT effects is of greater current interest and strongly suggests the complementarity of these traditionally opposed forms of therapy.

The spectrum between hot and cold: anhedonia, warm cognition, motivation

At first sight the processes of hot cognition appear very different from the cold cognition that has already been described. However, while these extremes may appear qualitatively distinguishable at a clinical level, a clear gradient intervenes to join extremes of emotional experience through to emotionally valenced decision and motivation. When we refer to absence of motivation we imply the absence of the stimulus/incentive to act or react in a certain way. Purposeful behavior is motivated behavior, which means that either physiological or social stimuli activate or motivate a person to do something. The neuroscience of this kind of behavior is a major current interest, quite independent of its implications for studying clinical depression.\(^22\) The current understanding can be sum-
**Functioning in Depression: A Major Challenge**

Clinically, the recognition that both the depressed state and the recovery after depression may involve more than one dimension (of clinical symptoms) remains novel. Instead, absent pleasure and loss of vigor are often assumed to co-vary. The structure of normal emotion instead would predict differential recovery. Anhedonia is probably the psychopathological construct that best reflects the pleasure domain. It means the absence of pleasure from acts that would normally be pleasurable. However, it has received relatively little attention in clinical research despite being prominent as an item in the diagnosis of major depression (item 2 in Table I). The Snith-Hamilton Pleasure Scale (SHAPS) attempts to capture the pleasure likely to be experienced under a range of conditions (watching TV, being with family or friends, hobbies and pastimes, favorite meal, warm bath or shower, etc). It is essentially a judgment of how things have recently been and it does not require actual participation in these activities. Nevertheless, it clearly tests a different experience from simply asking about depressive symptoms and so is quite likely to differentiate from a scale like the HAM-D scale. Preliminary trials suggest that this is the case for agomelatine, compared with venlafaxine. Thus, agomelatine showed the same effect as venlafaxine on the HAM-D scale, but a better recovery on the SHAPS scale.

**Conclusions**

Cold cognition is an unexpected accompaniment of mood disorder. It is easy to measure and may be amenable to treatment. It is fundamental to our understanding of full recovery of function in major depression. Hot, or even warm, cognition is a construct that also encourages us to look beyond the simple symptoms of a depressed mood. In either case, cognitive function provides the stimulus to take a more sophisticated approach to understanding antidepressant action and the potential differences between antidepressants. The interest of neuroscientists in the structure of emotional experience and learning means that there are relatively simple experiments that will allow the dissection of warm cognition in laboratory settings. Warm cognition can be tested in a more mechanistic way than the simple experience and observation of emotion could allow. It is a first step to more personalized diagnosis and treatment of mood disorder and a more complete restoration of function.

**References**

Impression of cognitive symptoms and anhedonia on functioning in depression – Goodwin

Keywords: anhedonia; antidepressant; cognition; major depression; treatment

**RÔLE DES SYMPTÔMES COGNITIFS ET DE L’ANHÉDONIE SUR LE FONCTIONNEMENT DANS LA DÉPRESSION**

Il est pratique de distinguer la cognition associée aux émotions, parfois appelée la cognition chaude, de la cognition froide qui est associée à des actes de mémoire, de calcul, de planification ou d’exécutions des tâches compliquées mais essentiellement sans émotions. Il n’est pas surprenant que la cognition froide soit faussée par des états d’humeur extrêmes comme la dépression majeure et la manie, mais il n’en est pas forcément de même pour la cognition chaude. En fait, le rôle important de l’altération de la cognition froide est maintenant établi empiriquement pour la dépression majeure, avec le problème qui y est lié, le ralentissement psychomoteur. Néanmoins, les méthodes standard de mesure réelles issues de la neuropsychologie ne constituent pas une norme de soin en psychiatrie. Elles le deviendront probablement, car les symptômes persistants des troubles épisodiques de la mémoire et de la diminution de la motivation sont sûrement liés à l’expérience subjective de l’anhedonie. De plus, ils limitent la possibilité d’un guérison fonctionnelle complète de la dépression majeure. D’après des études expérimentales chez l’homme et l’animal, les troubles cognitifs de la dépression sont au moins partiellement reversibles sous antidépresseurs. Une amélioration des résultats de la dépression majeure serait donc possible en ciblant la cognition plutôt que simplement les symptômes dépressifs. La compréhension du trouble de l’humeur s’est concentrée sur la cognition chaude. Le traitement cognitivo-comportemental a été élaboré pour répondre de façon spécifique aux distorsions cognitives négatives extrêmes de l’état dépressif. On considère habituellement que son efficacité sur les mécanismes cognitifs signe leur place fondamentale dans la maladie. Une deuxième question se pose : comment fonctionnent les antidépresseurs sur des processus presque similaires ? Les études de motivation et de récompense des neurosciences nous ayant appris qu’il existe un pont entre les cognitions chaudes et froides, la distinction entre les différentes composantes de l’émotion peut être étudiée plus facilement et subtilement, en particulier pour l’anhedonie et la contribution du plaisir à une guérison fonctionnelle complète.

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While there is considerable consensus about first-line treatments of major depressive disorder and anxiety and related disorders, there is ongoing controversy about the nature of, and approach to, subsyndromal and residual symptoms of these conditions. Such symptoms deserve attention for a number of reasons, including their association with impairment and relapse, and in this paper, recent developments in this area of work are briefly reviewed. Conceptually, it makes good sense to regard depression and anxiety disorders as chronic disorders that are deserving of a staged and sequential approach to assessment and management. Further, several randomized controlled trials have been useful in showing that targeted pharmacotherapy or psychotherapy interventions are useful for specific residual symptoms. At the same time, there is a relative lack of data in this area, and clinicians should also exercise clinical judgment to ensure optimal diagnosis and management of subthreshold and residual symptoms.

Subthreshold and residual symptoms

It has long been recognized that in efficacy studies many patients with depression do not respond fully to pharmacotherapy, psychotherapy, or their combination, a fact underlined by recent effectiveness trials (Figure 1). Work in this area was given further impetus by the development of operational definitions for recovery, remission, relapse, and recurrence of depression. More recent contributions have further refined these concepts (Table I, page 454), and also extended them to other disorders. Subsequent studies have emphasized the impairment associated with subthreshold mood and anxiety symptoms. In particular, community studies, which allow rigorous investigation of a broad spectrum of symptomatology, have indicat-
ed that clinical thresholds may have a degree of arbitrariness, given that respondents with symptomatology that fails to meet diagnostic criteria, but that is severe and persistent, suffer significant impairment. Indicators of such impairment include a range of measures such as disability, suicidality, and use of health care resources. 13

Clinical studies have complemented this work by emphasizing the significance of residual depressive and anxiety symptoms. First, residual symptoms are associated with worse psychosocial impairment.14,15 Second, residual symptoms of depression are associated with greater risk of relapse and a more chronic course of illness.16,17 There are fewer data addressing this issue in anxiety disorders, but some suggest that similar relationships may hold.16,20 There are also relatively few studies addressing whether residual symptoms predict recurrence of disorders, but again there are some data suggestive of a significant association.21

Subthreshold prodromal symptoms may be related to residual symptoms of treatment; the “roll-back phenomenon” refers to observations that as an illness begins to respond and re-
Remission
- Should become a primary end point in acute phase clinical trials
- Is present if for ≥3 weeks there is an absence of both sad mood and reduced interest and no more than three of the remaining seven symptoms of a major depressive episode (MDE) are present
- May be followed by recovery or recurrence only
- Day-to-day function is not part of the formal definition of remission, but is an important secondary outcome
- Symptoms that occur following remission that are insufficient to diagnose an MDE are ‘subsyndromal symptoms following remission’
- Trials that use remission as a primary outcome need to be of longer duration (12-20 weeks), with sufficiently frequent symptom assessments to establish the presence of remission
- Remission is not achievable for all depressed patients

Relapse
- Can only occur following remission but before recovery
- Requires that DSM-IV-TR diagnostic criteria for an MDE be met

Recovery
- Can only be declared after ≥4 months following the onset of remission
- Symptoms that do not meet DSM-IV-TR criteria for an MDE that occur following recovery are “subsyndromal symptoms following recovery”

Recurrence
- Requires the development of an MDE defined by DSM-IV-TR
- Can only occur following the onset of recovery

Relapse
- Empirically evaluate these recommendations
- Routinely provide survival curves to describe or compare outcomes across groups
- Report the number to treat
- Conduct and report moderator analyses
- Establish triage points to facilitate longer duration trials
- Compare different symptom scales
- Report secondary outcomes based on associated (non-criterion) symptoms, function, and quality of life

Table I. Recommendations of the ACNP task force on the conceptualization of remission.
Abbreviations: ACNP, American College of Neuropsychopharmacology; MDE, major depressive episode.

mit, those symptoms that first appeared are also the last to disappear.22 The notion that residual symptoms reflect underlying neurobiological deficits that precede onset of the full disorder, is supported by work emphasizing that antidepressant response has a slower time course than placebo response.23 Furthermore, if prodromal symptoms of relapse mirror those of the initial episode, then early recognition of such symptoms may be particularly useful.24

The literature on subthreshold and residual symptoms has made an important contribution to emphasizing that mood and anxiety disorders are chronic conditions, and so require both short- and long-term individual and public health interventions. Shorter-term treatment should clearly aim at response, remission, and relapse prevention.26 Longer-term management should likely aim at recovery, arguably at well-being, and certainly at recurrence prevention.24

Nature of residual symptoms
Various investigations have attempted to delineate the prevalence and type of residual mood and anxiety symptoms. One- to two-thirds of patients with major depressive disorder fail to respond fully to antidepressant treatment of adequate dose and duration,26-27 Anxiety, sleep impairment, fatigue, and cognitive disturbances are particularly frequent residual symptoms of depression, and many patients with residual symptoms have multiple such symptoms (Figure 2).14 Residual symptoms include both core depressive symptoms (eg, suicide) as well as less classical symptoms of depression (eg, pain).27 Residual anxiety may be a particularly robust predictor of relapse.24

Some research has addressed the question of how best to assess residual symptoms. Assessment of recovery should arguably cover the domains of symptoms, psychosocial impairment, and pathophysiological changes.28 Depression rating scales, the Sheehan Disability Scale, and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire may be useful,29 as may the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).30

It is also important, however, to differentiate treatment-emergent side effects from residual symptoms, and to address any comorbid psychiatric or medical disorders that may confound symptom assessment.26 Other relevant clinical and diagnostic issues to consider include antidepressant tachyphylaxis, inaccurate diagnosis (eg, missing bipolar disorder), and lack of adherence (Table II).31 It is also important to consider relevant psychosocial stressors; there is evidence that patients with residual symptoms are particularly vulnerable to depression when exposed to life stressors.24

A number of studies have contributed to understanding the neurobiology of residual symptoms.32-33 Several systems have been studied in patients in recovery from depression. First, such patients demonstrate alterations in the hypothalamic-pituitary-adrenal axis. Second, some patients demonstrate abnormalities in the serotonergic system, with increased vulnerability to depressive symptoms after tryptophan depletion. Third, there may be persistent shortened rapid eye movement (REM) latency and evidence of decreases in cortical γ-amino butyric acid (GABA). Finally, there may be persistent negative biases in the processing of emotional material. Several of these disturbances, including dexamethasone suppression, electroencephalographic sleep abnormalities, and cognitive
biases, have been associated with increased risk of relapse. Nevertheless, it should be noted that few studies directly link such abnormalities with residual symptoms.

**Treatment of residual symptoms**

Despite the clinical significance of residual depressive and anxiety symptoms, the evidence-based literature on the management of such symptoms is relatively sparse. Thus, expert consensus in this area continues to rely on clinical wisdom and anecdotal experience. A few randomized controlled studies have, however, addressed specific interventions for particular residual symptoms. Furthermore, there is a growing literature on the management of treatment-resistant depression and anxiety disorders, which may be relevant.

A first approach to the management of residual depressive or anxiety symptoms is to target specific symptoms based on presumptive underlying neurobiology or known treatment approaches. Thus, for example, zolpidem augmentation may be useful in improving residual insomnia, and modafinil augmentation may be useful in improving residual fatigue in patients treated with antidepressants for major depressive disorder. Prazosin or cognitive-behavioral therapy augmentation may be useful for residual sleep impairment in posttraumatic stress disorder. Augmentation studies also demonstrate benefit for clonazepam augmentation of antidepressants for anxiety in depression, and of eszopiclone augmentation of antidepressants for insomnia in generalized anxiety disorder. While a range of other agents may be considered along these lines, only a few options are supported by data from randomized controlled trials addressing residual symptoms in treated patients.

A second approach is to assume that residual symptoms represent incomplete treatment, and so to use the most robust possible augmentation and switch approaches. A range of evidence-based pharmacological augmentation options are now available for the management of treatment-resistant depression and anxiety disorders. Furthermore, augmentation with cognitive-behavioral therapy has also been shown to be effective in a range of these conditions.

Switching to a different pharmacological class has long been recognized as a valuable option, although success rates are not always as high as clinicians would like. This approach would seem particularly compelling when patients have a history of multiple relapse and recurrence with severe prodromal and residual symptomatology. It may also be particularly relevant when particular residual symptoms are thought to respond to specific pharmacological or psychotherapeutic interventions.

Indeed, it is important to differentiate subthreshold and residual symptoms. There are several different relevant considerations here. First, while residual symptoms may predict relapse, other well-known predictors including the number of previous episodes, stability of response, and adequacy of treatment should not be ignored. Second, data on antidepressant efficacy are more persuasive for severe symptoms of depression, while it is generally harder to differentiate medication from placebo in the management of mild symptoms. It is relevant to mention that only atypical antipsychotics and L-methylfolate are FDA-approved for use as adjunctive agents in depression, and that the former are associated with a sig-

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**Table II. Differential diagnostic issues in evaluating new-onset or residual symptoms in major depressive disorder.**

<table>
<thead>
<tr>
<th>Issue</th>
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<tbody>
<tr>
<td>Antidepressant tachyphylaxis</td>
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<tr>
<td>Side effects of/interactions with other medications</td>
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<tr>
<td>Psychosocial factors</td>
</tr>
<tr>
<td>Inaccurate diagnosis</td>
</tr>
<tr>
<td>Comorbid medical disorders</td>
</tr>
<tr>
<td>Comorbid psychiatric disorders</td>
</tr>
<tr>
<td>Lack of adherence leading to discontinuation syndrome</td>
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</tbody>
</table>

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*aBased on the American Psychiatric Association’s Practice guideline for the treatment of patients with major depressive disorder (3rd ed.)*

Figure 2. Residual symptoms following acute remission from major depressive disorder.

nificant adverse event burden. Third, while there is general agreement about the operationalization of response, remis-

sion, and even recovery, there is less agreement about the operationalization of constructs such as well-being. Some-
times, no treatment is the best form of management.26

As noted earlier, focusing on residual symptomatology may, however, be clinically useful in emphasizing that depression
and anxiety disorders are chronic conditions that deserve both short- and long-term individual and public health interventions.

In particular, they raise the issue of a staged approach to the assessment and management of these conditions. Anec-
dotally, experience, for example, suggests that for many patients a two-stage sequential approach may be useful, with pharma-
cotherapy for acute depression being followed by cognitive-
behavioral therapy for residual symptoms and relapse preven-
tion.24 There is a need for additional rigorous work in this area, following along the lines of that which has already been un-
dertaken for treatment-resistant mood and anxiety disorders.

**Conclusion**

Subthreshold and residual symptoms are important clinical phenomena insofar as they are associated with significant
impairment and predict relapse and recurrence. A body of liter-

ature has emphasized ongoing neurobiological abnormalities in patients in recovery from depression, but further work
is needed to relate such abnormalities to residual symptoms. Conceptually, it makes good sense to regard depression and

anxiety disorders as chronic disorders that are deserving of a

staged and sequential approach to assessment and man-

agement. Certainly, several randomized controlled trials have

been useful in showing that targeted pharmacotherapy or psy-

chotherapy interventions are useful for specific residual symp-

ptoms. At the same time, there is a relative lack of data in this

area, and clinicians should also exercise clinical judgment to
e

sure optimal diagnosis and management of subthreshold and

residual symptoms.

**Acknowledgment:** Prof Stein is supported by the Medical Research Council of South Africa.

**References**

1. Weissman MM, Klerman GL. Follow-up of depressed women after


depressed outpatients requiring one or several treatment steps: a STAR*D re-


3. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consen-
sus definitions of terms in major depressive disorder. Remission, recovery, re-

4. Pallanti S, Hollander E, Bienstock C, et al. Treatment non-response in OCD: me-


response and remission in major depressive disorder. Neuropsychopharmacology.

2006;31(9):1841-1853.


7. Judd LL, Schetter PJ, Akiskal HS. The prevalence, clinical relevance, and pub-


8. Fehm L, Beesdo K, Jacobb F, Fiedler A. Social anxiety disorder above and below

the diagnostic threshold: prevalence, comorbidity and impairment in the gen-


10. Tomino RL, Scheider EM, Trull TJ, Brown WC, Wood PK. Alcohol use among indi-

viduals with comorbid borderline personality disorder and posttraumatic


11. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Prevalence and Axis I co-

morbidty of full and partial posttraumatic stress disorder in the United States:

results from Wave 2 of the National Epidemiologic Survey on Alcohol and Re-


associated with subthreshold depressive conditions: a systematic review. BMC


14. Zajecka J, Komstten SG, Blier P. Residual symptoms in major depressive disor-


414.

15. Nerenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed pa-


chiatr Suppl. 1994;28(37-41.

17. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major de-


18. Stein DJ, Bandelow B, Gollberg OT, Andersen HF, Baldwin DS. Anxiety symp-


81-88.


er analysis of placebo-controlled continuation studies with escitalopram in ma-

jor depressive disorder, generalized anxiety disorder, social anxiety disorder,


duloxetine treatment for patients with generalized anxiety disorder. Hum Psy-

chopharmacol. 2011;26(3):258-266.

21. Paykel ES. Partial remission, residual symptoms, and relapse in depression. Dia-


1971.

23. Quitkin MF, Raskin GJ, Markowitz MJ, et al. Use of pattern analysis to identify


24. Fava GA, Ruini C, Belizae C. The concept of recovery in major depression. Psy-


25. Thase ME. Effectiveness of antidepressants: comparative remission rates. J Cln


Psychopharmacol. 2006;20(3 suppl):29-34.

27. Kurian BT, Greer TL, Trivedi MH. Strategies to enhance the therapeutic efficacy


8(7):975-984.

28. Israel JA. Remission in depression: definition and initial treatment approaches. J

Psychopharmacol. 2006;20(3 suppl):5-10.

29. Zajecka JM. Residual symptoms and relapse: mood, cognitive symptoms, and


30. McIntyre RS. Using measurement strategies to identify and monitor residual


31. American Psychiatric Association. Practice guideline for the treatment of pa-


32. Bhagwagar Z, Cowen PJ. ‘It’s not over when it’s over’: persistent neurobiologi-

cal abnormalities in recovered depressed patients. Psychol Med. 2008;38(3):

307-313.

33. Trivedi MH, Hollander E, Nue D, Blier P. Clinical evidence and potential neu-

robiological underpinnings of unresolved symptoms of depression. J Cln Psy-

chiatry.
Un large consensus existe sur le traitement de première intention des épisodes dépressifs majeurs et de l’anxiété et des troubles qui y sont liés alors que la nature de leurs symptômes résiduels, des symptômes légers et l’approche qui en est faite font toujours débat. Ces symptômes méritent l’attention pour plusieurs raisons, dont leur association avec une incapacité et une rechute ; cet article passe rapidement en revue les dernières avancées dans ce domaine. Cela semble logique en théorie, la dépression et les troubles anxieux étant des maladies chroniques nécessitant une approche séquentielle et graduelle dans l’évaluation et la prise en charge. Au demeurant, plusieurs études contrôlées randomisées ont montré l’utilité des traitements psychothérapeutiques ou pharmacologiques dans les symptômes spécifiques résiduels. Parallèlement, il existe un manque relatif de données dans ce domaine et les médecins doivent se servir de leur sens clinique pour un diagnostic et une prise en charge des symptômes résiduels et infra-liminaire les meilleurs possibles.
Depression is associated with disability, increased mortality—including (but not mainly) from suicide—poorer outcomes from physical illness, and greater use of primary and secondary and social care resources. Despite this, most controlled evaluations of antidepressants and other treatment interventions focus on change in depressive symptoms. It has been suggested that the benefits of antidepressants decrease with age and are no longer clinically significant in the population aged over 65. This paper argues that it would be more appropriate to design clinical trials to focus on change in function rather than on change in depressive symptoms. Parameters relevant to function are identified. These include the tolerability of the treatment, its impact on quality of life (both overall and disease-related), its effects on cognitive functioning, whether it reduces health care costs, whether it prevents relapse and recurrence, and whether it can prevent full-blown depression if given to older people at high risk. The evidence regarding each of these parameters is briefly reviewed. Antidepressants do appear to be quite well tolerated by older people. They are also effective in preventing relapse and recurrence. There is little information on the impact of antidepressant treatment on health care costs, though more complex treatment packages do appear to be cost effective. Preventative approaches show promise in terms of both effectiveness and cost-effectiveness. There is a dearth of evidence regarding measures designed specifically to measure functional response in older depressed patients.
older people since most early antidepressant trials in old age excluded most of the people presenting for treatment because of the near ubiquity—particularly in the "older-old"—of physical comorbidity.

However, despite clinical trials in older people having become more pragmatic, most still adopt symptom relief as the primary outcome measure. Although the two most recently published clinical trials have been positive,2,3 and the largest and most recent meta-analysis to date4 has also shown overall benefits for antidepressants in older people, the effect sizes are often small. One recent meta-analysis5 has suggested that the benefits of antidepressants decrease with age and are no longer clinically significant in the population aged over 65. The authors emphasized that there were relatively few studies in the over 65 population, that the studies did include were quite heterogeneous, and that functional aspects such as physical comorbidity and executive dysfunction might have had a particularly adverse effect on outcomes in the 65+ studies.

In view of the apparently modest clinical effects as conventionally measured and the profound effects of depression in old age on day-to-day functioning, it would surely be more appropriate to design clinical trials to focus on change in function rather than on change in depressive symptoms. What components of "function" might be relevant if such an approach were adopted? I would argue that these should include the tolerability of the treatment (in terms of side effect and withdrawal rates), its impact on quality of life (both overall and disease-related), its effects on cognitive functioning (which might be beneficial or adverse), whether it reduces health care costs, whether it prevents relapse and recurrence, and whether it can prevent full-blown depression if given to older people at high risk. Though the evidence base examining effects on these broader parameters remains limited, many of the more recent clinical trials have provided evidence related to functional efficacy and effectiveness. In this paper I will attempt to give a brief overview of that evidence, and thereby highlight the need for further research on the extent to which treating depression in old age can ameliorate clinical functioning. This review focuses particularly on trials of antidepressants (Table I, page 460), though some relevant studies involve psychological treatments and/or examine care packages rather than focusing exclusively on antidepressant treatments alone.

**Tolerability**

Older depressed people almost invariably have one or more physical illnesses. Many are also taking prescribed (or over-the-counter) medications for these illnesses, which may cause adverse interactions when antidepressants are coprescribed. More fundamentally, the pharmacokinetic and pharmacodynamic changes associated with ageing can significantly alter the propensity of antidepressant medication to cause clinically significant side effects. These changes include decreases in lean muscle mass and in passive drug absorption, increases in body fat, and thereby in the elimination half-life of (fat soluble) antidepressants.6 Changes in binding proteins mean that free circulating levels of selective serotonin reuptake inhibitors (SSRIs) are increased but those of tricyclics are lowered. There are also age-related decreases in drug metabolism and excretion. What is less clear is the extent to which these potential problems are clinically significant.

In clinical practice, SSRIs are in fact generally well tolerated by older people, though gastrointestinal (GI) problems such as nausea are common.7 It is not clear, however, whether nausea is more common in older than in younger patients. SSRI-related GI bleeding is potentially important in older people since they are in any case at greater risk of such bleeding and are very often coprescribed anti-inflammatory drugs, which carry a high risk of GI bleeding. Other SSRI-related side effects, which may be clinically more relevant in old age, include restlessness, sedation, extrapyramidal movement disorders, and hypotension, though the latter is usually mild. Drug interactions involving the cytochrome P450 enzyme system may be clinically relevant in older people; citalopram, escitalopram, and sertraline may carry a relatively low risk in this regard. In the context of clinical trials, adverse event–related withdrawal (AERW) rates may provide the best overall measure of real-life tolerability. Such AERW rates are generally low, though venlafaxine has been found to have a relatively high rate5 (27%, compared with 19% for fluoxetine and 9% for placebo in a three-arm study). Agomelatine, vortioxetine, and duloxetine have all recently been reported as carrying similar risks of AERW to placebo, though in the three-way comparison between vortioxetine, duloxetine, and placebo,5 duloxetine had a slightly higher AERW rate (10% vs 6% on vortioxetine and 3% on placebo).

**Cognition**

Cognitive dysfunction is an important component of depression in older people that may significantly contribute to functional disability. Cognitive deficits may precede the onset of the depression. Though some degree of cognitive improvement usually accompanies recovery from a depressive episode, the cognitive deficits do not always reverse completely. Persisting

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AERW</td>
<td>adverse event–related withdrawal</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>HTA-SADD</td>
<td>Health Technology Assessment Study of the use of Antidepressants for Depression in Dementia</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Improving Mood-Promoting Access to Collaborative Treatment (study)</td>
</tr>
<tr>
<td>IPT</td>
<td>interpersonal psychotherapy</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>SDS</td>
<td>Sheehan Disability Scale</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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</table>

The challenge of restoring functioning in older depressed patients – Katona

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cognitive dysfunction may be a prodromal indicator of future dementia. Antidepressant medication may have adverse effects on cognitive function—as was particularly evident in the case of tricyclic antidepressants because of their high anticholinergic potency and the relative lack of cholinergic reserve in the ageing brain.

The notion that newer antidepressants might actually enhance cognition independently of their antidepressant effects is a potentially exciting one. Raskin et al.\(^{13}\) hypothesized that the serotonin–norepinephrine reuptake inhibitor duloxetine might enhance cognition because of its dual action (blocking reuptake of noradrenaline as well as serotonin). Unusually, their trial was designed with the primary aim of testing this hypothesis and included subjects with mild dementia. The authors developed a trial-specific composite cognitive score using tests previously shown to be most impaired in depression. Their results confirmed that duloxetine improved cognitive function compared with placebo and—more importantly—that the effects of depression were largely (more than 90%) independent of the antidepressant effects that were also evident. More recently these findings were replicated in a three-way comparison between duloxetine, vortioxetine (which has multiple serotonin-enhancing effects), and placebo.\(^{3}\) Both duloxetine and vortioxetine had beneficial (and largely direct) effects on acquisition and delayed recall. Vortioxetine also enhanced speed of processing. Neither study examined whether the effects they identified were clinically significant. Cognitive

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial type</th>
<th>Number of participants</th>
<th>Care setting</th>
<th>Patient characteristics</th>
<th>NNT if available</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson(^{2})</td>
<td>Review 10 placebo-controlled randomised trials of 2nd generation ADs</td>
<td>4165</td>
<td>Out-patients</td>
<td>&gt;60 years Nonpsychotic unipolar major depression</td>
<td>11</td>
<td>Overall modest benefit Longer response times needed in older population</td>
</tr>
<tr>
<td>Mukai(^{2})</td>
<td>Review 18 trials, head-to-head and placebo-controlled trials of single vs dual-action ADs</td>
<td>4942</td>
<td>In- and out-patients</td>
<td>&gt;59 years Major depressive disorder (MDD)</td>
<td>n/a</td>
<td>No evidence of additional benefit of dual vs. single action ADs Low response and remission rates for active treatment</td>
</tr>
<tr>
<td>Sneed(^{2})</td>
<td>Review 16 studies – 9 comparator, 7 placebo-controlled</td>
<td>3122</td>
<td>Out-patients</td>
<td>&gt;59 years Unipolar major depression</td>
<td>n/a</td>
<td>Variability of results between comparator vs placebo-controlled trials – patients’ expectation may lead to diminished response in placebo-controlled studies</td>
</tr>
<tr>
<td>Kok(^{4})</td>
<td>Review of 51 RCTs</td>
<td>3394</td>
<td>In- and out-patients</td>
<td>MDD, Dysthymia, minor depression, sub-clinical or sub-threshold depression not otherwise specified</td>
<td>6.7 for response 14.4 for one additional remission</td>
<td>Overall superiority of ADs vs placebo No difference between AD classes demonstrated</td>
</tr>
<tr>
<td>Tedeschi(^{5})</td>
<td>Review 74 RCTs, 59 adult and 15 late-life</td>
<td>4935</td>
<td>In- and out-patients</td>
<td>MDD, Adult group: &lt;65 years, Late-life group: ≥55 years</td>
<td>n/a</td>
<td>Superiority of ADs vs placebo not statistically significant in 65+ age group Relatively small number of trials in 65+ available</td>
</tr>
<tr>
<td>Katona(^{3})</td>
<td>Three-arm RCT of vortioxetine (VOR), duloxetine (DUL) and placebo (PLA)</td>
<td>452</td>
<td>Psychiatric, psycho-geriatric and geriatric settings</td>
<td>≥65 years Baseline HAM-D(24) =29</td>
<td>Response vs placebo: VOR 5.6 DUL 3.6 Remission VOR 10.1 DUL 6.5</td>
<td>Vortioxetine and duloxetine superior to placebo</td>
</tr>
<tr>
<td>Heun(^{2})</td>
<td>Placebo-controlled trial of agomelatine</td>
<td>222</td>
<td>Out-patients</td>
<td>≥65 years Moderate to severe recurrent MDD</td>
<td>Response 4.8 Remission 14.5</td>
<td>Superiority of agomelatine on both depressive and global outcome scales</td>
</tr>
</tbody>
</table>

**Table I. Main findings of recent efficacy trials.**

**Abbreviations:** AD, antidepressant; DUL, duloxetine; HAM-D, Hamilton Depression Scale; MDD, major depressive disorder; n/a, not applicable; PLA, placebo; RCT, randomised controlled trial; VOR, vortioxetine.

function has also been examined in a recent trial (Health Technology Assessment Study of the use of Antidepressants for Depression in Dementia [HTA-SADD]) of sertraline and mirtazapine against placebo for depression in Alzheimer’s disease. Neither active antidepressant had significant effects on cognition as measured by the Mini Mental State Examination (MMSE) score.

**Impact on quality of life**

Raikin et al. examined the effect of duloxetine on a specific aspect of quality of life: pain. They found duloxetine superior to placebo in relieving back pain and total time spent in pain. Similar trends were found for other pain modalities that did not reach statistical significance. This study did not use an overall quality of life measure. The HTA-SADD trial examined both generic and dementia-related quality of life in patients with the depression of Alzheimer’s disease and found that neither active drug had significant effects on quality of life. In the IMPACT study (Improving Mood-Promoting Access to Collaborative Treatment), which evaluated stepped collaborative care delivered by a care coordinator based in primary care and supporting the patient’s regular primary care clinician, the active intervention showed benefits both in terms of a global measure of quality of life and in terms of function as measured with the Sheehan Disability Scale (SDS). Though this scale has work, social life, and family life subscales, only total scores were reported.

To the best of my knowledge, the only recent trial that has used a function-focused measure of quality of life in evaluating a novel antidepressant on older people is the agomelatine/placebo study by Heun et al. Like the IMPACT study, this study incorporated the SDS scale. Agomelatine was associated with improvement in all three (work, social life, and family life) subscales. The authors did not comment on the extent to which these effects were independent of agomelatine’s antidepressant effects.

**Effect on health care costs**

Katon et al. found that total outpatient and inpatient costs were about 50% greater for depressed than for nondepressed older patients after allowing for comorbid chronic medical conditions. Most of the costs related to physical rather than mental health care. In the light of this, it is surprising that most recent antidepressant treatment trials in older people do not report on associated health care costs. One exception is the HTA-SADD study of mirtazapine and sertraline in the depression of Alzheimer’s disease, which found that although neither antidepressant was effective, mirtazapine was nonetheless cost effective in terms of reducing informal carer costs. This probably reflected its sedative effect.

More complex treatment packages for elderly depressed patients have, however, been subjected to detailed cost analysis, particularly in the United States. Integrated care (ie, care provided in the primary care setting by a behavioral health professional co-located in that setting) was compared with enhanced specialist referral. The integrated care model was found to be cost effective (in terms of number of “depression-free days”) in the Veterans Affairs setting but not in other settings. In keeping with this, a follow-up of the IMPACT study concluded that the intervention evaluated (a stepped collaborative care program based in primary care and supporting the patient’s regular primary care clinician) was associated with sustained costs as well as clinical benefits over a 4-year follow-up.

A stepped care approach to preventing depression in the primary care setting in Holland (discussed in the section on prevention below) has also been shown to be cost effective, based on willingness to pay €5000 for an extra depression- or anxiety-free year. The cost effectiveness (like clinical effectiveness) of such an approach was not, however, demonstrated in an attempted replication in the nursing-home context.

**Prevention of relapse and recurrence**

Most short- and longer-term studies indicate that antidepressants reduce relapse and recurrence rates in patients who have achieved remission on the antidepressant in question. This was clearly demonstrated in high-risk patients (ie, those with several previous episodes) for the tricyclic antidepressant nortriptyline (with or without adjunctive interpersonal psychotherapy [IPT]). These findings were replicated for the SSRI paroxetine (again with and without IPT), though the latter study included patients who were not at particularly high risk of relapse.

Kok et al. carried out a systematic review that aimed to include all double-blinded placebo-controlled randomized controlled trials with antidepressant continuation or maintenance treatment of unipolar depression in patients aged over 55 years. They excluded studies restricted to patients with bipolar depression, psychotic depression, or depression in the context of specific medical disorders. They also examined tolerability in terms of AERW rates. The authors identified 11 published trials that met their entry criteria. The effect of drug treatment was consistent across the studies. The absolute risk of suffering a relapse or recurrence using antidepressants compared with placebo was reduced by 28%, and the number needed to treat (NNT) to prevent one relapse or recurrence using antidepressants compared with placebo was reduced by 28%, and the number needed to treat (NNT) to prevent one relapse or recurrence using antidepressants compared with placebo was reduced by 28%, and the number needed to treat (NNT) to prevent one relapse or recurrence using antidepressants compared with placebo.
ticular promise in older people because of the high prevalence of subsyndromal depression in this population and the particularly strong association between old age depression and excess mortality from stroke, myocardial infarction, and cancer.

Schoevers et al\(^2\) identified the following older people as being at greatest risk of depression and therefore at greatest risk of benefitting from preventative interventions: those with functional limitation as a result of disability such as stroke or macular degeneration, those with limited social networks, and those with subsyndromal depressive symptoms. They concluded that the group in whom prevention might be achieved most efficiently would be those with subsyndromal depressive symptoms.

The evidence to date supports these conclusions. A meta-analysis (not restricted to older people) found that overall, preventative interventions reduced the new incidence of major depression by about 20%.\(^2\)\(^7\) A more recent review focusing on preventative trials in older people found that several interventions showed promise.\(^2\)\(^8\) These included:

- Social support for people who have been spousally bereaved
- Multicomponent interventions for dementia caregivers
- Problem-solving therapy in people with medical illnesses
- Antidepressants following stroke
- Stepped-care prevention in primary care

Evidence published since that review has provided further support for the use of some of these interventions. The incidence of depression following stroke was effectively prevented both by low-dose escitalopram and by problem-solving therapy (PST) with an NNT of about 8 for both interventions.\(^2\)\(^9\) In primary care patients with subsyndromal anxiety or depression symptoms aged 75 or over, a stepped-care approach was associated with caseness-level incident depression or anxiety in only 11% at 1 year, compared with an incidence of 24% in controls treated as usual. A more recent set of studies has, however, failed to confirm either the clinical benefits or the cost effectiveness of the stepped-care approach in the care-home (as opposed to the community) setting.\(^2\)\(^2\)

Reynolds et al\(^1\) have carried out a detailed conceptual review of the potential benefits of early intervention focusing on whether such benefits might be evident in low- and middle-income as well as in high-income countries. They concluded that relatively simple learning-based psychological approaches such as problem-solving therapy may be a particularly attractive option in low- and middle-income countries. The authors expressed misgivings about the preventative use of antidepressants (in contexts other than relapse and recurrence prevention), given the limited evidence for their efficacy in mild depression and the increased vulnerability to antidepressant-related adverse effects (such as falls and hyponatremia) associated with the ageing process. They also highlighted the promise of biomarkers (such as proinflammatory cytokines) in identifying those at highest risk, and of the potential benefits of systematic collection of data on clinical risk markers such as insomnia, social isolation, and physical disability.

**Conclusions**

Some of the more recent clinical trials of antidepressants and of other interventions have evaluated outcome measures that are more relevant to clinical functioning than changes in depressive symptoms. However, the evidence base for most of these measures is limited. Antidepressants do appear to be quite well tolerated by older people—with some antidepressants showing AERW rates similar to those of placebo. The evidence indicating that antidepressants are effective in preventing relapse and recurrence in patients who remit following initial treatment is also robust.

In contrast, there is little information on the impact of antidepressant treatment on health care costs, though more complex treatment packages do appear to be cost effective. Preventative approaches show promise in terms of both effectiveness and cost effectiveness, but more research is needed. There is a dearth of evidence regarding measures designed specifically to measure functional response in older depressed patients. In this regard, the recent evaluation of agomelatine against placebo by Heun et al\(^2\) provides a good precedent for future studies.
La dépression est associée à un handicap, à une augmentation de la mortalité, y compris (mais pas majoritairement) par suicide, à une moins bonne évolution au décours des maladies et à une plus grande utilisation des ressources des soins primaires, secondaires et sociaux. Malgré cela, la plupart des évaluations contrôlées des antidépresseurs et des autres traitements s’intéressent aux modifications des symptômes dépressifs. Les bénéfices des antidépresseurs diminueraient avec l’âge et ne seraient plus cliniquement significatifs au-delà de 65 ans. Cet article préconise de mettre en place des études cliniques centrées sur les modifications du fonctionnement plutôt que sur les modifications des symptômes dépressifs. Les paramètres se rapportant au fonctionnement sont connus, ils comprennent la tolérance au traitement, son influence sur la qualité de vie (globale et liée à la maladie), ses effets sur le fonctionnement cognitif, l’incidence sur la diminution des dépenses de santé, la prévention éventuelle des rechutes et récidives et la prévention possible d’une dépression authentique chez des sujets âgés à haut risque. Les données disponibles pour chacun des paramètres sont brièvement analysées. Les personnes âgées semblent bien tolérer les antidépresseurs qui préviennent aussi rechutes et récidives. L’impact des traitements antidépresseurs sur les dépenses de santé est peu documenté quoique les associations plus complexes de traitements semblent réduire les coûts. Les approches préventives sont prometteuses en termes d’efficacité et de rapport coût/efficacité. Les données sont rares en ce qui concerne les mesures spécifiques de la réponse fonctionnelle chez les patients âgés déprimés.

Keywords: antidepressant; depression; function; old age

RESTAURER LE FONCTIONNEMENT DES PATIENTS ÂGÉS DÉPRESSIFS : UN VÉRITABLE ENJEU

La dépression est associée à un handicap, à une augmentation de la mortalité, y compris (mais pas majoritairement) par suicide, à une moins bonne évolution au décours des maladies et à une plus grande utilisation des ressources des soins primaires, secondaires et sociaux. Malgré cela, la plupart des évaluations contrôlées des antidépresseurs et des autres traitements s’intéressent aux modifications des symptômes dépressifs. Les bénéfices des antidépresseurs diminueraient avec l’âge et ne seraient plus cliniquement significatifs au-delà de 65 ans. Cet article préconise de mettre en place des études cliniques centrées sur les modifications du fonctionnement plutôt que sur les modifications des symptômes dépressifs. Les paramètres se rapportant au fonctionnement sont connus, ils comprennent la tolérance au traitement, son influence sur la qualité de vie (globale et liée à la maladie), ses effets sur le fonctionnement cognitif, l’incidence sur la diminution des dépenses de santé, la prévention éventuelle des rechutes et récidives et la prévention possible d’une dépression authentique chez des sujets âgés à haut risque. Les données disponibles pour chacun des paramètres sont brièvement analysées. Les personnes âgées semblent bien tolérer les antidépresseurs qui préviennent aussi rechutes et récidives. L’impact des traitements antidépresseurs sur les dépenses de santé est peu documenté quoique les associations plus complexes de traitements semblent réduire les coûts. Les approches préventives sont prometteuses en termes d’efficacité et de rapport coût/efficacité. Les données sont rares en ce qui concerne les mesures spécifiques de la réponse fonctionnelle chez les patients âgés déprimés.
Some somatic medical illnesses can lead to depression, and depression can be a risk factor for the development of various medical illnesses. Moreover, depression can manifest through somatic symptoms and mimic other diseases. Comorbidity between depression and a somatic medical illness is very frequent and is a confounding factor that hampers and reduces the rate of diagnosis of depression—and consequently its treatment—thus contributing to increased health care costs.

Medical comorbidities and functioning in depression: a clinical perspective

Although very common, the comorbidity between depression and various somatic illnesses is frequently neglected and undertreated in clinical practice. Those affected often consult a general practitioner, a medical professional that is usually ill-equipped to recognize depression or establish a hierarchy between the comorbid conditions, and so the somatic illness often becomes the main target of investigation and treatment. This difficulty in recognizing the comorbidity between a somatic illness and depression has consequences for the clinical outcome, since comorbidity between depression and somatic illnesses is a downward spiraling condition, where each illness (depression and the somatic illness) becomes a risk factor for the other. There is accumulating evidence implicating inflammation as a critical mediator in the pathophysiology of depression. In fact, depression can both trigger inflammatory processes and be triggered by inflammation. As many comorbid illnesses are also inflammatory in nature, it is likely that inflammation could be the common underlying mechanism in at least some of these comorbidities, like depression with cardiovascular illnesses or diabetes, among many others. This article briefly reviews the main aspects of the comorbidity between depression and somatic illnesses. In particular, it addresses the challenge represented by its recognition and reviews the available evidence showing the role played by inflammation.

Medicographia. 2014;36:464-469 (see French abstract on page 469)

Psychiatric disorders have a unique nature that makes them seem different from other medical conditions. They are often poorly understood, perhaps because they have both a biological and a psychological aspect, even though their psychological aspect actually has a biological basis. Physicians are trained in biology since the beginning of their medical studies, and for them understanding the nature of psychiatric disorders—depression among them—can be a challenge. This challenge is greater because some somatic medical illnesses can lead to depression, and depression can be a risk factor for the development of various medical illnesses. Moreover, depression can manifest through somatic symptoms and mimic other diseases. Comorbidity between depression and a somatic medical illness is very frequent and is a confounding factor that hampers and reduces the rate of diagnosis of depression—and consequently its treatment—thus contributing to increased health care costs. Understanding the nature of this higher-than-expected association is the first step to motivating the physicians that are most likely to see such patients—i.e., general practitioners—to improve their skills in diagnosing and...
treated depression. On the other hand, from a psychiatric point of view, studying the comorbidity between depression and somatic illnesses offers an opportunity to address the possible mechanisms underlying not only this interaction, but also mood disorders. This review will briefly expose some important aspects of this comorbidity, in particular the challenge represented by its recognition and the evidence suggesting that inflammation is a possible mechanism underlying this interaction.

**Medical comorbidity is common in depression**

As expected, the co-occurrence between two very common conditions—depression and other nonpsychiatric medical diseases—is itself only common due to statistical chance. This fact alone is justification enough to study this subject, since these comorbidities change the prognosis and treatment of both conditions. But this is only part of the problem. In fact, through mechanisms that are still poorly understood, a variety of nonpsychiatric medical conditions are risk factors for the development of depression. Similarly, through mechanisms that are now beginning to be unravelled, depression is a risk factor for the development and progression of a variety of nonpsychiatric medical illnesses, like diabetes and cardiovascular diseases, among others. Therefore, these interactions increase the prevalence of these comorbidities.

To exemplify this, a large epidemiological study using data collected by three German statutory health insurers during the period 2005-2007 showed that 99.8% of “severe depressive patients” (defined as ICD-10 F32.2, F32.3, F33.2, and F33.3, n=110,462) also presented a “somatic comorbidity.” On the other hand, looking from the cardiological perspective, another meta-analysis showed that inflammation is a possible mechanism underlying not only this interaction, but also mood disorders. This review will briefly expose some important aspects of this comorbidity, in particular the challenge represented by its recognition and the evidence suggesting that inflammation is a possible mechanism underlying this interaction.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>IL-1</td>
<td>interleukin 1</td>
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<tr>
<td>IL-6</td>
<td>interleukin 6</td>
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<tr>
<td>INF-α</td>
<td>interferon-α</td>
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<tr>
<td>TNF-α</td>
<td>tumor necrosis factor alpha</td>
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Chronic pain (of at least 6 months’ duration) has also been recognized as a common comorbidity with depression. A large survey including 18,980 subjects interviewed by telephone showed that at least one chronic painful physical condition occurred in 43.3% of subjects with major depression, four times more frequently than expected.

**Depression often goes unrecognized in depressive patients with a medical comorbidity**

The first medical professional consulted for the diagnosis and treatment of patients showing depression and somatic illness comorbidity is often a general practitioner or another medical specialist with no psychiatric training. Often, these professionals investigate and treat the somatic illness, while depression is either unrecognized or considered secondary. This was demonstrated in a population-based survey in which only about half of the patients suffering from a major depressive disorder were diagnosed as such by a regular health care professional.

Another study showed that only 23.1% of depressive patients received this diagnosis when consulting a primary care physician, patients with moderate depression being less likely to be diagnosed (17.8%) than those with moderately severe or severe depression (30.8% and 49.4%, respectively).

Depression is more often the unrecognized “side” of the comorbidity when the physician consulted is a general practitioner, which seems logical because the training and experience of general practitioners are more directed toward diagnosing and treating somatic illnesses than psychiatric disorders. This problem cannot be solved easily. Of course, training in the
The recognition of depressive symptoms and syndromes could help improve the rate of diagnosis of depressive episodes. However, since many patients presenting with depression may, in fact, be suffering from bipolar disorder, prescribing the correct treatment requires the ability to differentiate between the two conditions. The use of antidepressants without mood stabilizers in patients with bipolar disorder could be harmful, which is why training in the diagnosis and treatment of depression must be balanced with training in the diagnosis and treatment of bipolar disorder in order to improve interventions and outcomes.

Somatic symptoms impair the recognition of depression

When they consult their physician, patients complain of signs and symptoms, which are then used by the physician to direct the investigation. Therefore, from a practical point of view it is important to study the relationship between somatic symptoms, and not only the somatic diagnosis, but also the co-occurrence of depression. Moreover, somatic symptoms are not synonymous with somatic illnesses, since they may be experienced by depressive patients in the absence of a somatic illness. This was exemplified in a large collaborative study organized by the World Health Organization involving 1146 major depressive patients who were consulting in primary care facilities in 15 different cities in 14 countries and underwent structured assessment for depressive and somatoform disorders. An average of 69% major depressive patients reported only somatic symptoms when consulting their general practitioner (ranging from 45% in Paris to 95% in Ankara), an average of 50% of them complained of unexplained somatic symptoms (ranging from 30% in Mainz to 62% in Bangalore), and an average of 11% denied having any psychological symptom (ranging from 2% in Rio de Janeiro to 26% in Athens and Berlin). Therefore, depression could mainly be described by patients through somatic symptoms, making its diagnosis more difficult, especially in the primary care setting, and leading these patients to use the health care system frequently.

Another variable that seems important is the number of somatic symptoms that appear to be associated with depressive and anxiety disorders. In primary care, the prevalence of mood disorders in patients with 0 to 1, 2 to 3, 4 to 5, 6 to 8, and 9 or more somatic symptoms was respectively 2%, 12%, 23%, 44%, and 60%. The majority of depressive patients will first consult a general practitioner. In general, such patients complain of somatic symptoms to their doctor not least because he/she is trained to inquire about and investigate somatic signs and symptoms. This scenario, together with the fact that depression may be accompanied by somatic symptoms, may lead to a failure to recognize depression and result in a time-consuming investigation that will not resolve the patient’s suffering and will increase health care use, and consequently, costs.

Comorbid depression increases the risk and worsens the outcome of medical conditions

Comorbidity is defined as two or more medical conditions existing simultaneously in the same patient. They can exist independently or interact, one being a risk factor that triggers or promotes further progression of the other. An example of such an interaction is the association of depression following myocardial infarction with mortality. A meta-analysis that included patients with myocardial infarction showed that depression was significantly associated with all causes of mortality (OR, 2.38; 95% CI, 1.76-3.22), cardiac mortality (OR, 2.59; 95% CI, 1.77-3.77), as well as new cardiovascular events (OR, 1.95; 95% CI, 1.33-2.85). Another meta-analysis studied different aspects of the relationship between depression and coronary heart disease. Depression was identified as a risk factor for the occurrence of coronary events in previously healthy subjects (OR, 1.81; 95% CI, 1.53-2.15) as well as a risk factor for a worse prognosis (OR, 1.8; 95% CI, 1.50-2.15).

Another example is provided by comorbidity between depression and diabetes. In a study in which 10 704 patients with diabetes were surveyed over a 2-year period, it was shown that the occurrence of depression increased the risk of all-cause mortality by approximately 36%. In a prospective cohort 4184 patients were surveyed for approximately 5 years. Baseline major depression was associated with increased all-cause mortality (hazard ratio [HR], 2.26; 95% CI, 1.79-2.85), cardiovascular mortality (HR, 2.0; 95% CI, 1.37-2.94), and with noncardiovascular and noncancer mortality (HR, 3.35; 95% CI, 2.30-4.89), while minor depression showed a similar tendency. As explained above, the interaction between depression and somatic illness could be a “two-way street,” one being a risk factor for the other and vice-versa. In relation to this, a prospective 5-year follow-up study was conducted to identify risk factors for the occurrence of major depression in diabetic patients. It found that one or more coronary procedures during the follow-up period (OR, 1.92; 95% CI, 1.14-2.25) or the number of diabetes symptoms at baseline (OR, 1.14; 95% CI, 1.05-1.22) were predictors of having major depression at the end of the follow-up. Thus, comorbidity could be viewed as a downward spiral, where both sides are risk factors for the other and can worsen the outcome.

Somatic diseases may lead to depression

Generally, the first approach regarding the high prevalence of depression associated with somatic diseases is based on the fact that illness can cause intense and constant stress and suffering capable of triggering and maintaining depression. The exception would be a disease whose biological mechanism has been found to cause depression, such as central nervous system and endocrine diseases. For example, it is easy to understand why Parkinson’s disease is associated with the development of major depression since, aside from the physical impairment associated with this disease, there is a decrease in dopamine levels that could provoke depres-
sion or some of its symptoms.\textsuperscript{20} It is important to note that the stress and hopelessness brought about by a chronic and progressive disease that alters one’s lifestyle, diminishes one’s capacity in many domains, causes limitations, and affects one’s self-esteem may itself trigger depression.

Perhaps a better example is hypothyroidism, which occurs in about 15% of patients with depression, a level of prevalence that is much higher than expected.\textsuperscript{21} Thyroid hormone treatment may accelerate and augment antidepressant pharmacotherapy and greatly influence brain function via genomic and nongenomic effects. The genomic action of triiodothyronine (T\textsubscript{3}) regulates genes encoding neurotransphins and other proteins that are involved in intracellular signaling pathways, while the nongenomic action of T\textsubscript{3} involves activation of the phosphatidylinositol-3-kinase protein pathway, reduction of sensitivity of 5-HT\textsubscript{1A} autoreceptors (thereby increasing serotonergic neurotransmission) and increases 5-HT\textsubscript{2} receptor sensitivity;\textsuperscript{22} all events linked to the neurobiology of depression. Even “subclinical” hypothyroidism, which imposes few or no “somatic-related” limitations, shows a higher prevalence of depression,\textsuperscript{23} demonstrating that the mechanisms involved are the direct effect of thyroid hormones.

Recently, other disease mechanisms capable of triggering and sustaining a depressive syndrome have been discovered. One example is the inflammatory mechanisms that are present in many somatic diseases.\textsuperscript{1} Historically speaking, the relationship between depression and tuberculosis is a classic example. More recently, a syndrome called “sickness behavior,” which is characterized by anhedonia, anorexia, cognitive impairment, decreased libido, fatigue, psychomotor retardation, social withdrawal, and hyperalgesia, symptoms that are present in depression and are also typical of viruses among other diseases, has been described. Sickness behavior is caused by the action of some proinflammatory cytokines in the central nervous system, such as tumor necrosis factor alpha (TNF-\textalpha), interleukin 1 (IL-1), and interleukin 6 (IL-6), among others.\textsuperscript{24} Many other conditions such as cardiovascular diseases, diabetes, cancer, asthma, or rheumatologic diseases, all of which are related to an increased prevalence of depression, also increase proinflammatory cytokines.

\textbf{Stress induces inflammatory mechanisms}

Some powerful risk factors for the development of depression, like early life stress and adulthood life stress, are associated with elevated inflammation.\textsuperscript{25} One example is provided by a study in which 135 adolescent girls were examined in relation to the production of IL-6 at baseline and following a major life event. Those subjects raised in a harsher family environment produced greater levels of IL-6 in comparison with those raised in a less harsh family environment.\textsuperscript{26} Moreover, stressful early life events are associated with higher levels of inflammation during a depressive episode. In a large cohort study, 1037 individuals were included from birth and surveyed for 32 years. Subjects with depression and no childhood maltreatment did not show any statistical difference in C-reactive protein (CRP) levels when compared with controls levels. However, subjects with childhood maltreatment as well as those with maltreatment plus depression showed a statistical increase in CRP when compared with controls.\textsuperscript{27}

As mentioned above, a considerable amount of research shows that adulthood life stress is also associated with elevated inflammation. Both acute and chronic stress may elicit inflammation, particularly those events involving social stressors like conflict, threat, isolation, and rejection.\textsuperscript{28} This is exemplified by a study in which elderly adults who recently experienced the death of their spouse were shown to have higher levels of IL-1 and IL-6 activity than nonbereaved elderly adults. This response was moderated by a specific genotype of the IL-6 gene.\textsuperscript{29} Another example is provided by a study in which adolescent girls at high risk for depression were assessed regarding rejection-related life events and leukocyte levels of mRNA for proinflammatory transcription factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and inhibitor of kB (I-kB) (which regulates the effect of NF-kB). They found that the mRNA levels of both NF-kB and I-kB were higher in adolescents that had experienced a rejection situation than in those that had not.\textsuperscript{30}

\textbf{Depression can be triggered by inflammation}

One argument that suggests that inflammation is a risk factor for the development of depression is the fact that about 50% of patients using interferon-\textalpha (INF-\textalpha) developed a major depressive episode.\textsuperscript{29} However, the other 50%, although they showed some neurovegetative symptoms like psychomotor retardation, fatigue, and disrupted appetite or sleep, cannot be said to have developed a major depressive episode because they did not develop affective or cognitive symptoms such as depressive mood, feelings of worthlessness, or guilt.\textsuperscript{29} In addition, having experienced a prior depressive episode has been shown to be a predictive factor for developing depression following INF-\textalpha use.\textsuperscript{28} Therefore, it seems that inflammation could trigger depression in vulnerable people.\textsuperscript{24}

\textbf{Depression could also be an inflammatory disease}

In the last ten years we have observed increased interest in inflammatory mechanisms mediating the etiology and progression (related with prognosis) of mood disorders in general.\textsuperscript{1,20,24} There is now substantial data showing that different inflammatory processes are activated in depression. For example, the circulating levels of several proinflammatory cytokines including IL-1, IL-6, and TNF-\textalpha, as well as CRP are higher, and there are increased numbers of T-cells bearing T-cell activation markers, including CD4+ and CD8+, increased production of interferon-\gamma (IFN\gamma), and elevated levels of the soluble receptors for IL-2 and TNF-\textalpha.\textsuperscript{23,24} It is important to point out that some of these inflammatory processes can diminish the availability of the serotonin precursor, tryptophan, a fact
that may also contribute to triggering depression or to decreasing the effect of selective serotonin reuptake inhibitors for example.1,2

Do inflammatory mechanisms play a role in comorbidity? As mentioned above, early life stress and adulthood stress elicit inflammatory processes; moreover, depression can both trigger inflammatory processes and be triggered by inflammation. Finally, many frequent comorbid illnesses are also inflammatory in nature. Therefore, inflammation could be at least one reason (among others, as yet unidentified) for the higher-than-expected frequency of comorbidity between these somatic conditions and depression. In other words, inflammation (besides psychological stress) could play a key common role in the pathophysiology of some of these comorbidities and depression.2,4

Does medical comorbidity impair functioning and recovery from depression? The short answer is yes. As mentioned above, inflammatory medical comorbidities can cause sickness behavior, the typical symptoms of which (anhedonia, anorexia, cognitive impairment, decreased libido, fatigue, psychomotor retardation, social withdrawal, and hyperalgesia) are also widely seen in depression. Sickness behavior is induced by some proinflammatory cytokines in the central nervous system—such as TNF-α, IL-1, and IL-6, among others3,5—and not only impair functioning, but also hampers recovery from depression since it contributes to the maintenance of residual depressive symptoms. Moreover, the restraint and burden that somatic diseases entail may be a risk factor that can trigger and maintain depression and impair recovery. The mechanisms involved here are multiple and not fully understood, but may, in part, be due to activation of the hypothalamic-pituitary-adrenal axis, which is recognized as a key element for triggering depression. Given this, medical comorbidities could be considered as an element that worsens functioning and impairments full recovery from depression.

Conclusion Comorbidity between depression and somatic illnesses is simultaneously highly prevalent and widely neglected. Those affected usually first consult general practitioners, who frequently fail to recognize depression or establish a hierarchy between the conditions. Therefore, the somatic illness usually becomes the main target of investigation and treatment. On the other hand, in addition to psychological distress, pain, and physical limitations, which have always been accepted as causes for the development of depression concomitantly to a medical disease, in the last ten years the role of inflammation as a common mechanism underlying some of these comorbidities has been investigated and identified. This leads us to ask why these interactions are so frequently encountered and why such comorbidities can be seen as a downward spiraling condition, where both depression and the somatic illness mutually contribute to the other as risk factors and ultimately worsen the outcome for the patient.

References
14. Roseberht JD, Cha DS, Mansur RE, McIntyre RS. Infrared moods: A review of
the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2014;53:23-34.


Keywords: comorbidity; cytokine; depression; functioning; inflammation

Comorbidités médicales et fonctionnement dans la dépression : un point de vue clinique

Bien que très courantes, les comorbidités entre dépression et maladies somatiques sont souvent négligées et sous-traitées en pratique clinique. Les sujets concernés consultent fréquemment un médecin généraliste, dont les compétences sont souvent peu adaptées à reconnaître une dépression ou à hiérarchiser les comorbidités, la maladie somatique devenant souvent la cible principale des examens et du traitement. Cette difficulté à distinguer la comorbidity entre maladie somatique et dépression n’est pas sans conséquence sur l’évolution clinique puisque cette comorbidity est une spirale descendante dans laquelle chaque pathologie (la dépression et la maladie somatique) devient un facteur de risque pour l’autre. De plus en plus de données mettent en cause l’inflammation comme médiateur essentiel dans la physiopathologie de la dépression. En fait, la dépression peut à la fois déclencher un processus inflammatoire ou être déclenchée par l’inflammation. De nombreuses comorbidités étant de nature inflammatoire, l’inflammation pourrait probablement être le mécanisme commun sous-jacent de certaines d’entre elles, telles la dépression et les maladies cardiovasculaires ou le diabète, parmi beaucoup d’autres. Cet article décrit les principaux aspects de la comorbidity entre dépression et maladies somatiques, abordant en particulier la difficulté inhérente à sa reconnaissance et analysant les données disponibles sur le rôle joué par l’inflammation.
In this article we review functional and structural brain imaging studies in major depression, the brain effects of antidepressants, and their relationship with psychosocial functioning. Major depression is characterized by altered dynamics in neural networks involved in emotion and cognitive functions. Among these networks, the default mode network (DMN) has been extensively studied in major depressive disorder (MDD). The DMN is a network comprising anterior and posterior medial regions of the brain involved in self- and other-processing, autobiographical memory, and allocation of attentional resources to the internal and external world. Several studies have showed that the anterior part of the DMN—the dorsomedial prefrontal cortex—and the posterior part of the DMN—the precuneus—are respectively associated with rumination and autobiographical memory impairment in MDD. Both rumination and autobiographical memory problems may contribute to functional impairment in depression and increase the duration of a depressive episode. By normalizing the cooperation between networks, antidepressants contribute to restoring the homeostatic balance between emotional and cognitive processes in depressed patients, thereby promoting functional recovery.

Major depressive disorder (MDD) is a leading cause of functional disability that represents a tremendous burden for patients, families, and health care systems. Sobocki et al estimated the total annual cost of depression in Europe at €118 billion. Direct costs alone totaled €42 billion, and indirect costs due to morbidity and mortality were estimated at €76 billion. Overall, this makes major depression one of the most costly brain disorders in Europe. Several factors may contribute to functional impairment in depressed patients, including symptom severity, acute and persistent cognitive-emotional problems, and medical comorbidities. Moreover, MDD is associated with a high rate of recurrence, and almost 30% of depressed patients develop treatment-resistant depression.

Based on its chronic and episodic course, MDD may be conceptualized as a neurodevelopmental disorder impacting the function and structure of multiple neural networks. In this short review we will discuss the structural and functional brain changes observed in MDD, the brain effects of antidepressant treatment, and the putative relationships between these brain changes and psychosocial functioning.
Functional brain changes in major depressive disorder

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies of cerebral blood flow and glucose metabolism in major depression have consistently revealed that depression is a system-level disorder affecting discrete—but functionally integrated—cortical, subcortical, and limbic networks. Resting-state studies of depressed patients have identified alterations in the ventral and dorsal medial and lateral prefrontal cortex, ventral and dorsal anterior cingulate, posterior cingulate, parietal cortex, basal ganglia, insula, amygdala, and hippocampus prior to treatment. In a resting-state fMRI study of depressed patients the dorsomedial prefrontal cortex (DMPFC) was found to exhibit increased connectivity to seed regions representative of the cognitive (parietal and lateral prefrontal cortices), default mode (medial prefrontal and parietal cortices), and affective networks (amygdala), suggesting altered neural network dynamics in major depression.

The dorsomedial prefrontal region and other regions involved in MDD are constitutive elements of the default mode network (DMN). The DMN is a network comprising ventral and dorsal medial prefrontal regions, the hippocampus, and the medial parietal (precuneus) and posterior cingulate regions. Although its specific function is not clearly defined, the DMN is involved in self- and other-processing, autobiographical memory, and allocation of attentional resources to the internal and external world. The DMPFC—the anterior part of the DMN—is activated during self-referential processing tasks, where subjects have to relate neutral or emotional stimuli to themselves. In keeping with the hypothesis of abnormal self-processing in MDD, impaired activation (usually increased activation) of the DMPFC has been described in depressed patients (Figure 1).

Rumination, a process characterized by increased and repetitive self-focus on negative content, is a clinical hallmark of impaired self-processing in MDD. There is evidence that rumination is associated with increased connectivity in the DMN, both in healthy subjects and in depressed patients. In a study involving treatment-naïve patients with first-episode depression, Zhu et al observed increased connectivity of the DMN in patients compared with controls, and found that the activity of the anterior part of the DMN (ie, DMPFC) was positively correlated to rumination scores. There is a large body of observational and experimental evidence suggesting a reciprocally reinforcing relationship between rumination and negative affect. Moreover, levels of rumination have been associated with the severity of depressive episodes in depressed patients. Moreover, increased levels of rumination have been found to increase social withdrawal, dampen executive resources, and contribute to psychosocial functioning impairment in MDD.

The precuneus—the posterior medial part of the parietal cortex—is also a core element of the DMN. At rest, the precuneus is highly connected with other regions of the DMN, but it is also connected with the lateral prefrontal cortex (cognitive network) when subjects are engaged in cognitive tasks. Thus, the precuneus is a hub that regulates cognition, emotion, and behavior.

Several studies have shown that the precuneus is involved in the physiopathology of depression. In the study with treatment-naïve patients with first-episode depression discussed above, the posterior part of the DMN (ie, the precuneus) was hypo-connected in depressed patients and was correlated with overgeneralization (OGM) during autobiographical memory tasks.
memory retrieval. OGM emphasizes the difficulty of depressed patients to retrieve specific (ie, spatio-temporal, factual, and emotional details) personal memories in response to retrieval cues. We demonstrated elsewhere that patients with acute depression show impaired autobiographical memory.26 Nixon et al described hyperconnectivity in the DMN and hypogyrification of the precuneus in remitted depressed patients.29 Although Nixon et al did not assess autobiographical memory performance, their results may confirm the findings of Bergouignan et al,27 which showed impaired autobiographical memory retrieval in remitted depressed patients. Likewise, the abnormal structure and function of the precuneus in depression may be related to Freton et al’s findings in healthy volunteers, which showed that the gray matter volume of the precuneus is positively correlated with the ability of subjects to retrieve specific autobiographical events with a field perspective. Overall, in relation with other regions (especially the hippocampus; see below), the precuneus may subserve some aspects of autobiographical memory impairment in major depression. Autobiographical memory retrieval is a self-related process that contributes to the regulation of emotion. Impairment of such a process in acute and remitted major depression decreases the ability of depressed patients to adapt to the emotional and cognitive demands of their environment.

Greicius et al found increased resting-state functional connectivity of the precuneus and the thalamus compared with the rest of the DMN in depressed patients, and this increase was correlated with the duration of the depressive episode.29 Although Greicius et al did not assess self-related processes such as rumination and autobiographical memory retrieval in their population of depressed patients, several studies have highlighted the role of rumination and OGM in increasing the duration and risk of recurrence of depression.30,31

Beyond impaired self-processing, neuropsychological studies have consistently reported that depression interferes with effortful processing and that cognitive impairment may mediate psychosocial impairment in depressed patients.32 In healthy subjects, fMRI experiments indicate that increasing cognitive demand engages a pattern of brain activation that is characterized by a balance between increasing activity in cortical cognitive areas and decreasing activity in the DMN network.33 Patients with depression fail to modulate the activity of the medial prefrontal regions and the DMN in response to cognitive demand, suggesting that abnormal DMN and cognitive network interactions subserve performance decrements in effortful cognitive tasks in depression.34

Structural brain changes in major depressive disorder

Functional changes in major depressive disorder are associated with structural changes in areas involved in cognition and emotion processing, including the prefrontal cortex, orbito-frontal cortex, and subcortical regions.35 The hippocampus is a major region where structural changes occur in MDD. There is now a lot of evidence showing that MDD is marked by a reduction in hippocampal volume.36 Several factors contribute to this reduction in hippocampal volume: genetics, life-stress exposure (ie, physical or sexual abuse), the number of depressive episodes, inflammation, and hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis.

The volume of the hippocampus is usually reduced by 8% to 20%, with more pronounced changes in the posterior part of the hippocampus (head and tail; Figure 2).37 The exact molecular and cellular mechanisms involved in hippocampal damage and their histopathological signatures in depression are not clearly understood. Chronic stress exposure, glutamatergic toxicity, reduction in the density of glial cells and dendritic arborization, impairment in neurogenesis-related processes have all been proposed to contribute to impaired neuroplasticity in MDD.38 Studies in animal models combining MRI imaging and histopathological assessment are clearly needed to throw light upon the respective contributions of these mechanisms to hippocampal atrophy in MDD.

What are the functional consequences of structural hippocampal changes in depression? Longitudinal studies have shown that a reduction in hippocampal volume is associated with the persistence of depressive symptoms after 3 years of follow up and that it is a predictor of poor clinical outcome.39,40 On the other hand, patients with residual symptoms showed a higher decrease in hippocampal volume during clinical follow up.41

Young et al found that the autobiographical memory problems experienced by depressed patients was related to abnormal functional activation of the hippocampus.42 Likewise, episodic and working memory deficits have been found to be associated with hippocampal volume reduction in MDD.43

The links between structural and functional brain changes in depression have not been extensively investigated. One study showed that hyperconnectivity in the DMN was associated
with hypo-gyrification of the precuneus in remitted depressed patients with recurrent depression. Such studies on the relationships between structural and functional changes are essential to understand the chronic and episodic course of MDD more precisely and to disentangle the contribution of acute and chronic brain factors involved in psychosocial impairment in depressed patients.

**Brain effects of antidepressant treatment**

Does antidepressant treatment correct the brain activity pattern identified in major depression and restore normal dynamic interactions in neural networks? To answer this question, we used a meta-analytical approach to examine the patterns associated with clinical improvement in depression in emotional activation studies using fMRI. Nine emotional activation fMRI studies involving a total of 126 patients were included in the meta-analysis using the activation likelihood estimation technique. Following treatment with antidepressant drugs, the activation of several brain regions involved in response to emotional stimuli in major depression was normalized. In addition, decreased activation in the anterior (BA 32) and posterior cingulate cortices, as well as in the precuneus, was found to reflect restored deactivation of the DMN (Figure 3).

Several studies have assessed the differences between treatment responders and nonresponders to identify the specific brain changes necessary to obtain a clinical response. Mayberg and colleagues examined the time course of the regional metabolic changes associated with fluoxetine treatment in depressed inpatients. The patients were divided into responders (reduction ≥50% on the Hamilton Depression Rating Scale [HAM-D]) and nonresponders after 6 weeks of treatment. Clinical response was associated with limbic-paralimbic and striatal metabolic decreases and brainstem and prefrontal, dorsal anterior cingulate, posterior cingulate, and parietal metabolic increases. The identical pattern of the brain changes seen in depressed patients responding to placebo or cognitive-behavioral therapy suggests a final common pathway for clinical response in depression.

However, the presence of unique specific changes in the brainstem and hippocampus in fluoxetine-treated patients, which were not observed with other treatments, supports the hypothesis that both treatment-specific and response-specific effects can be identified.

Brain imaging at baseline can be used to predict short-term and long-term clinical outcomes and functional recovery. Several studies have found that pretreatment metabolic activity in the rostral (pregenual) cingulate uniquely distinguishes medication responders from nonresponders. It is now generally accepted that clinical remission—defined as a HAM-D score of 7 or less—is the primary goal for the treatment of depression. Using remission as the end point of their study, McGrath et al found that anterior insula activity predicted clinical remission to antidepressant treatment or cognitive-behavior therapy. In a recent study in depressed outpatients treated with agomelatine, we were able to demonstrate that reduced activation of the DMPFC and precuneus at baseline during self-referential processing was a good predictor of clinical remission at 6 months.

**Conclusion**

Antidepressant treatments exert their therapeutic effect through modulation of the reactivity of the limbic, DMN, and cortical networks to cognitive and emotional stimuli as well as during the resting state. This is in agreement with the concept of major depression as a brain disorder of multiple connected neural networks and with the effects of conventional or atypical antidepressant treatments such as ketamine on these connected networks in healthy subjects. The mechanism of action of antidepressant treatment likely contributes to restoring the homeostatic balance between emotional and cognitive processes in depressed patients, thereby promoting functional recovery.
References

Nous analysons dans cet article les études d’imagerie cérébrale fonctionnelles et structurales dans la dépression majeure, les effets cérébraux des antidépresseurs et leur relation avec le fonctionnement psychosocial. La dépression majeure est caractérisée par une modification de la dynamique des réseaux neuronaux impliqués dans l’émotion et les fonctions cognitives. Parmi ces réseaux, le réseau du mode par défaut (RMD) a été largement étudié dans l’épisode dépressif majeur (EDM). Le RMD comprend les régions cérébrales médianes antérieure et postérieure impliquées dans les processus liés au Soi et à d’autres processus comme la mémoire autobiographique et la répartition de l’attention au monde intérieur et extérieur. Selon plusieurs études, la partie antérieure du RMD, le cortex préfrontal dorsomédian, et sa partie postérieure, le précunéus, sont associées respectivement à la rumination et à l’altération de la mémoire autobiographique dans l’EDM. Les problèmes de rumination et de mémoire autobiographique participeraient au déficit fonctionnel dans la dépression et augmentent la durée de l’épisode dépressif. Les antidépresseurs, en normalisant la coopération interréseaux, restaurent l’équilibre homéostatique entre les processus émotionnel et cognitif chez les patients déprimés et favorisent donc le rétablissement fonctionnel.
Although effective treatments for major depressive disorders are available, better treatments are needed. Personalized medicine may improve the outcomes of current treatments; its aim is to identify which characteristics of an individual can predict the outcome of a specific treatment in order to get a better match between the individual and the treatment received. In the past few years, several different approaches have attempted to develop personalized treatments. Pharmacogenetic studies have not yet been successful, but it is expected that combined data from genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology may eventually lead to effective personalized antidepressant treatments. Randomized trials comparing different therapies in specific target groups have resulted in some preliminary knowledge regarding who benefits from which treatment. For example, pharmacotherapy is probably more effective than psychotherapy in dysthymia, and combined treatments are more effective in older adults. New data mining techniques are now emerging that may constitute a new approach to personalized treatments. Finally, clinical staging has been proposed as a model for personalized treatment of depression. Although there is little evidence as yet that it will indeed lead to better outcomes, it is a good framework to guide our thinking about personalized treatments. However, it is clear that much more research is needed before all of these different approaches lead to personalized treatments that can be used in practice.

Major depressive disorders constitute one of the great challenges for health care in the next decades. Major depression is currently ranked fourth worldwide in terms of disease burden, and is expected to rank first in high-income countries by the year 2030. Depressive disorders are associated with a substantial loss of quality of life for patients and their relatives, huge economic costs, and an increased risk of dying.

It is well established that psychological and pharmacological therapies are effective in the treatment of adult depression. Several types of antidepressant medication have been found to be effective, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenalin reuptake inhibitors (SNRIs), and several others. Several hundreds of trials directly comparing different types of medication have also shown that all these medications are most likely to be about equally effective.
Several types of psychotherapy have also been shown to be effective, including cognitive behavior therapy, interpersonal psychotherapy, behavioral activation therapy, problem-solving therapy, counseling, and possibly psychodynamic therapy. Dozens of trials directly comparing different types of psychotherapy have also shown that there are no differences—or only small ones—between the effects of these therapies and that all therapies seem to be equally effective.

In addition, dozens of trials with direct comparisons between psychotherapies and pharmacotherapies have shown that psychotherapies and pharmacotherapies are equally effective or approximately equally effective. This suggests that all psychological and pharmacological treatments of adult depression are equally effective or about equally effective for mild to moderate depression, although this may not pertain to more chronic forms of depression and dysthymia.

Although these current treatments are considered to be effective, there is also much room for improvement. Modeling studies have shown that pharmacological and psychological treatments together can reduce the disease burden of depression in only about 33% of patients. More than 40% of patients do not, or only partially, respond to treatment and less than one-third of all patients have completely recovered after completing their treatment. Furthermore, relapse rates are estimated to be 50% after 2 years and up to 85% within 15 years after recovery from an initial episode. Therefore, it is very important to improve the outcomes of treatment.

So, we have several pharmacological and psychological treatments that are on average equally effective, but have only limited effects. The fact that these treatments are equally effective does not mean, however, that there are no differences in the response of individual patients to them. Individuals can vary widely in their response to specific treatments, and they may benefit from one treatment, but not from another. Ultimately, outcome research should not aim to answer the question of whether a treatment is effective, but rather the question: “what treatment, by whom, is most effective for this individual with that specific problem and under which set of circumstances?”

**Toward personalized treatments for depression**

One important way to improve the outcome of treatment in depression is to develop personalized treatments. “Personalized medicine” aims at identifying which characteristics of an individual will predict the outcome of a specific treatment in order to get a better match between the individual and the treatment received. These characteristics may include sociodemographic characteristics and clinical characteristics of the depressive disorder, as well as biological markers. The development of personalized treatments is considered by many to be one of the major challenges for health care research in the next decades. The development of personalized treatments for depression is especially important because at the moment there is very little evidence that, on average, one treatment of depression is more effective than another.

Although the overall effects of different psychological and pharmacological treatments are comparable, it is very likely that specific patients with specific characteristics may respond better to one treatment than to another. For example, preliminary research shows that pharmacotherapy is probably more effective than psychotherapy in patients with dysthymia and chronic depression, and combined treatments are more effective than each treatment alone in older adults and mental health outpatients. But overall, our knowledge of outcome predictors and moderators is very limited, and consequently it is largely unknown which individual patient will respond to which treatment.

Predictors can be defined as the characteristics that predict whether patients will respond to a treatment or not. Specific predictors indicate whether a specific characteristic predicts the outcome of therapy compared with a no-treatment control, while nonspecific predictors indicate variables that are related to improvement, regardless of comparison or control groups (within-group improvement). Moderators indicate whether participants respond better to one treatment than to another (examined in trials in which two treatments are directly compared with each other). For example, sex might not be a predictor (men and women might benefit equally from therapy) but it might be a moderator (women respond better to treatment X and men better to treatment Y). Research on moderators and predictors of outcome is of vital importance for the development of personalized treatments of depression.

**Personalized antidepressant medications and pharmacogenetics**

It has long been expected—especially in the field of pharmacogenetics—that the efficacy of pharmacological treatments could be improved by our increasing knowledge of genotype types, as about 50% of the response to antidepressants can be attributed to genetic factors. However, it has also become clear that the regulation of gene transcription and interactions between genes and environmental factors are extremely complicated. It should, therefore, not be expected that individual genetic information can easily be translated into personalized treatments for depression.
5-HT6), adrenoreceptor beta-1 and alpha-2, the dopamine receptors (D2), the G protein beta 3 subunit (GSK-3β), corticotropin releasing hormone receptors (CRHR1 and CRHR2), glucocorticoid receptors, c-AMP response-element binding protein, and brain-derived neurotrophic factor (BDNF). However, although there is some modest evidence that common genetic variations may contribute to individual differences in antidepressant response, no reliable predictors of antidepressant treatment outcome have been found until now.

There is also some evidence that genetic variations can contribute to variability in response to medication, with an impact on adverse effects. However, research on this topic has shown that the explained variance from single gene polymorphisms was actually very small, which again suggests that only combinations of various gene polymorphisms can contribute to individual variability in response to treatment. As yet, no large and replicable findings on the impact of genetic variations have been found.

It is expected, however, that in the future it will become possible to combine data from genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology and that this combined knowledge may lead to the development of effective personalized antidepressant treatment based on both genotypes and biomarkers.

Randomized trials in specific populations

It is not only in the field of pharmacogenetics that researchers are trying to develop personalized treatments for depression. Individual characteristics such as sociodemographic characteristics, clinical characteristics, and biological markers that could reliably predict differences in benefits or adverse effects in response to various depression treatments need to be identified.

Two types of study design could produce the evidence needed to identify characteristics that could lead to personalized treatment selection. In the first one, two treatments are compared in an unselected group of participants, and the researchers examine whether a specific characteristic of the participants moderates the relationship between treatment type and outcome. For example, in the NIMH (National Institute of Mental Health) Treatment of Depression Collaborative Research Program it was found that severity of depression at baseline could significantly predict differential treatment effects. Pharmacotherapy appeared to be more effective than psychotherapy in the more severely depressed patients, while there was no difference between pharmacotherapy and psychotherapy in the less severely depressed. In the second type of study design a group of patients with a specific characteristic is selected, and they are randomized to alternative treatments. For example, in a study among patients with multiple sclerosis it was found that cognitive behavior therapy was more effective than supportive-expressive group therapy.

It is important to note that if a study does not include a direct comparison between alternative treatments, it is not possible to identify moderators or predictors of differential treatment response. If, for example, a psychological treatment is compared with an untreated control group, a characteristic that significantly predicts outcome can be a true moderator, but it can also be a predictor of response to any treatment. So, only studies in which two or more treatments are directly compared with each other can be used to examine moderators of treatments.

In the past decades, many such comparative studies have been conducted in specific patient samples. Recently, we conducted a meta-analytic review of studies in specific target groups comparing antidepressant medication with psychotherapy, medication with combined treatment, and psychotherapy with combined treatment. The target group had to have a predefined sociodemographic characteristic, a specific type of depression, a comorbid mental or somatic disorder, or it had to come from a specific setting (outpatients, primary care). These studies can find evidence that psychotherapy, pharmacotherapy, or combined treatment is more effective in a specific target group. We included 52 studies with 4734 depressed patients. In these studies, 20 characteristics of the target groups were examined. The results showed that medication is probably the best treatment for dysthymia, and combined treatments are more effective in depressed outpatients, as well as in depressed older adults. However, in order to examine the 20 characteristics in the three categories of comparisons, 254 studies would be needed to have sufficient statistical power to show an effect size of g=0.5. Currently, only 20.1% of these studies have been conducted.

We concluded in our review that although a considerable number of studies have compared medication, psychotherapy, and combined treatments, and some preliminary results are useful for deciding which treatment is best for which patient, the development of personalized treatment of depression has only just begun and much more research is needed.

Decision trees and personalized treatment of depression

In the past few years a number of studies have used data mining techniques for the development of decision trees to predict who will benefit from a specific treatment or to choose between two treatments. In large samples of patients these techniques identify subgroups that benefit more or less from a specific treatment and these data are used to develop decision trees to determine who should get which treatment. For example, in one study of the STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression) it was found that the overall response rate to treatment was 47%, but that in the profiled patient subgroups the response rate ranged from 31% to 63%. In another study, classification and regression trees (CART analysis) showed that patients with HAM-D (Hamilton Depression scale) scores lower than 13 by day 7...
were more likely to be responders to fluoxetine or venlafaxine treatment than nonresponders. In a third recent example among inpatients with depression, it was shown that the presence of suicidality, a higher initial HAMD-21 total score, an episode length of less than 24 months, fewer previous hospitalizations, and absence of any ICD-10 F4 comorbidity were factors that predicted response to treatment.

A new method to predict differential response to various treatments was recently developed by DeRubeis and colleagues. Data from a previous randomized trial comparing cognitive behavior therapy with pharmacotherapy were used to identify pre-randomization variables that predicted differential response (marital status, employment status, life events, comorbid personality disorder, and prior medication trials). These variables were included in regression models aimed at the calculation of each patient’s Personalized Advantage Index (PAI). In 60% of the patients, one of the two treatments was predicted to be superior to the other treatment, and if all patients had been assigned to the optimal treatment the outcomes would have been significantly better (effect size d=0.58).

Although this approach is relatively new to the field of psychiatry and mental health, it can be expected that new applications of this approach will lead to meaningful decision trees that will result in personalized treatments and better outcomes for patients.

**Personalized treatment and clinical staging in depression**

Clinical staging can be seen as another attempt to develop personalized treatments for major depression. It is a tried and tested mode of diagnosis elsewhere in medicine, classifying complex diseases in terms of their stage of development. Major depression can also vary in individual patients from a single episode with minimal impact on the life course of the patient to a chronic relapsing disorder that causes lifelong and serious suffering or even premature death. The idea of clinical staging is that a treatment should be aimed at the specific stage that the patient is in. For example, an intervention aimed at a patient with subthreshold depression may be aimed at preventing further development of these symptoms into a full-blown major depressive disorder and could consist of a brief psychological training in cognitive behavioral skills.

On the other hand, an intervention aimed at a patient with chronic depression may involve a combination of pharmacotherapy and a psychological treatment specifically aimed at chronic patients. And a patient who has had several episodes of major depressive disorder may not only need acute treatment for a new episode, but also an intervention aimed at preventing relapse after a successful acute treatment.

Several possible advantages of clinical staging in depression have been proposed, such as a focus on prevention, a reduction of the heterogeneity of treatment response, and a move toward personalized treatments and away from the notion that all treatments are equally effective in all patients. Perhaps the most important benefit of staging is that it orients both clinicians and patients toward thinking about depression as a developmental disorder with a high risk of relapse and seeing it as a chronic disorder.

Until now there has not been sufficient evidence to show that clinical staging results in better outcomes of treatment, and although it is an interesting concept that helps to organize our thinking about depression, more research is needed to validate the different clinical phases and the differential effectiveness of treatments in these phases.

**Discussion**

Although effective treatments for major depressive disorders are available, their overall effects are limited and better treatments are needed. One way to improve the effects of current therapies is to develop personalized treatments. This is important because until now the evidence has shown that all psychological and pharmacological treatments are equally effective. At the same time, clinical practice shows that individuals respond better to one therapy than to another. Personalized medicine aims to identify which characteristics of an individual predict the outcome of a specific treatment in order to get a better match between the individual and the treatment received.

In the past years several different approaches have attempted to develop personalized treatments. Pharmacogenetic studies have not been successful yet, but it is expected that combined data from genomics, proteomics, metabolomics, neuroimaging, and neuroendocrinology may lead to the development of effective personalized antidepressant treatments. Randomized trials comparing different therapies in specific target groups have resulted in some preliminary knowledge regarding who can benefit from which treatment. For example, pharmacotherapy is probably more effective than psychotherapy in dysthymia, and combined treatments are more effective in depressed outpatients, as well as in depressed older adults. New data mining techniques are now emerging as another method to predict who will benefit from which treatment, and the first studies have shown that this may be a feasible approach to personalize treatments. Finally, clinical staging has been proposed as a model for personalizing the treatment of depression. Although there is little evidence as yet that this will indeed lead to better outcomes, it is a good framework to guide our thinking about personalized treatments.

One important problem for the development of personalized treatments of depression is that depression is a very heterogeneous disorder and that many different effective treatments are available. If we want to show that one treatment is better in an individual with a specific characteristic, we have to choose
between the many treatments that may be more effective than others in that individual. This implies that the number of trials that can be—and eventually will be—performed is very large. If we wanted to differentiate between the many available antidepressant medications and psychotherapies, and all possible combinations (in combined treatments), we would probably need many thousands of studies—only a fraction of which have so far been conducted—and millions of participating patients. This problem is multiplied if we focus on other characteristics that have not yet been examined in trials until now, such as biomarkers. And if we really want to develop personalized treatments for depression, we should not only look at individual characteristics of patients and treatments, but also at combinations of characteristics, such as older adults with atypical depression and a specific biomarker. Furthermore, we may want to look at other outcomes, such as side effects of medications, long-term outcomes, patient preferences, and prediction of treatment dropout rates. And we could also choose a more precise effect size of $g=0.3$ or even 0.2. This would require an almost endless number of randomized trials and even more patients who would be willing to participate in such trials. There is no doubt that the path toward personalized treatments is a long one, requiring considerable resources.

In conclusion, developing personalized treatments for depression is one of the most important challenges for mental health researchers in the next decades. There are several useful approaches that may, in the future, lead to giving personalized advice to patients about the treatment from which they will most likely benefit. In all of these different approaches it is clear that much more research is needed. There is no doubt, however, that the development of personalized treatments for depression has begun.
Personalized treatment for functional outcome in depression – Cuijpers
Depression is a multifaceted and etiologically complex disorder impairing both cognitive and emotional functioning. The contributors to this section draw on their clinical experience to discuss the optimal treatment of depression and the treatment targets for the complete relief of depressive symptoms. They also question whether depression can be fully treated and optimal global functioning restored.

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The word “cure” means permanently eliminating all the signs and symptoms of a given disease, by completely reversing the underlying pathogenetic mechanisms and thus restoring the patients’ premorbid health status and functioning. However, this is hardly true for depressive disorders. Residual symptoms are the rule after successful completion of pharmacological or psychotherapeutic treatment, and their presence has been correlated with poor outcome. The results of the STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) showed that the overall cumulative remission rate is far from satisfactory, and that after 12 months the majority of patients had relapsed. Although various treatments exist for the symptoms of depression, there is no known “cure” as defined above. There are several reasons contributing to the absence of a real instrumental cure.

First, depression is an etiologically complex disorder. Although there are converging lines of evidence suggesting that patients’ susceptibilities shaped by neurobiological factors such as corticotropin-releasing factor system and HPA-axis abnormalities, elevated inflammation-related cytokines, and decreased neurogenesis, as indicated by low levels of brain-derived neurotrophic factor (BDNF) may be associated with depression, the exact pathogenesis of depressive disorders is not fully understood. We are still awaiting biomarkers for depression to quantify the change in patients’ pathophysiological condition. Until validated and clinically interpretable biomarkers are available, no one will be able to conclude whether a depressive disorder is unequivocally “cured” or “not cured.” A patient who appears cured with ongoing treatment may still have an undetected, active, long-running illness. In contrast, in clinical studies some patients who do not meet the symptom-based definitions of remission nonetheless consider themselves in remission.

Second, several “gene-environment (stress) interaction” processes are known to be involved in the pathophysiology of depression and further contribute to its heterogeneous nature. The disease is not only heterogeneous, but is also often complicated with other medical and psychiatric comorbidities. Research is just beginning to understand the psychosocial factors such as upbringing, interpersonal relationships, or personality that moderate the expression of the biological mechanisms underlying depression. Psychological interventions specific to depression used in combination with antidepressant medication can improve treatment outcomes. It is unrealistic to hope for a “cure,” if the sufferer’s chronic stress is not addressed with psychosocial interventions and relevant socio-political actions.

Third, current treatment options do not effectively relieve the symptoms of depression. As yet, alternative and causative psychopharmacological treatment strategies beyond monoamine reuptake inhibition are unavailable. Recent research has shown that ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, leads to effects on the dysregulation of the glutamatergic system. Low-dose ketamine elicits an antidepressant effect in patients with major depression. These findings have fueled efforts to elucidate the mechanisms underlying ketamine’s antidepressant action as well as develop a new molecular understanding of depression. Thus, the development of novel, rapid-acting antidepressants yielding an outcome comparable to the definition of a “cure” must be a worldwide priority.

It is clear that we urgently need quantifiable biological markers to assess the underlying disease state and response to treatment and effective treatments that will bring a disease-free wellness state. Until then, “cure-oriented attitudes” to depressive patients won’t make much sense. The main goal of treatment should be “a complete and sustained remission” or “recovery” as defined by several investigators. A definition of recovery based on symptoms and psychosocial functioning should be pursued. Furthermore, the concept of recovery should involve an active role of the patient, and take into account his/her psychological well-being. Whether “recovery” absolutely means “cure” in terms of psychosocial and neurobiological variables should be a major topic for psychiatric care in the future.

References
Even though major depression ranks number one in years lost to disability (YLD) in the world, as defined by the World Health Organization, we have not yet established what we consider a cure; we treat until remission is reached.

The Oxford Dictionary defines cure and remission as follows:

◆ Cure: “eliminate (a disease or condition) with medical treatment”
◆ Remission: “a temporary diminution of the severity of disease or pain”

In major depression, only a few attempts have been made to define what is meant by “cure” and most of the definitions are still only symptom-based and not related to functioning or subtle symptoms.

The “American College of Neuropsychopharmacology (ACNP) task force on response and remission in Major Depressive Disorder” recommended in 2006 that recovery in major depression should be ascribed only after patients have remitted for at least 4 months. Most patients relapse within the first 4 months of remission, hence the recommendation. Others recommend waiting for 6 months of remission before recovery can be declared. Twelve long-term outcome studies have been published to guide us.

Major depression is a relapsing disorder, especially during the first few months following the onset of the disorder but it does not appear to be eventually chronic in the majority of patients.

Approximately 75% of patients relapse at least once with 20% relapsing at least 4 times. Most relapses occur within the first 2 years of the disorder. Remission is achieved in 50% of patients in the first 6 months and between 80% and 90% of patients are in remission after 5 years.

The World Health Organization recommends that antidepressants should be given for 9 months, while others recommend that antidepressants be continued for 26 weeks after remission. Studies reveal that functional impairment can persist for some time after remission and this often goes unrecognized.

The objective of treating depression would be to relieve the symptoms, to minimize the risk of suicide, to reduce the number of relapses, to reduce the time spent in a relapse, and to improve functioning. The average duration of major depression, if relapses and subtle symptoms are included, is of several years. Most patients fortunately reach remission eventually. Treatment should be preventative, and should therefore continue for at least 2 years, the time frame in which most relapses usually occur. If a treatment and preventative approach were followed, the prospect of a cure would be much more within reach of most patients earlier, suicide could be better prevented, and suffering reduced.

References
Is depression curable? The rigorous scientific answer must remain negative until we find the real “cause” and the means to eradicate it. The pragmatic answer for the clinicians is, however, more optimistic: with thoughtful and persistent use of our current therapeutic options most depressed patients respond to a meaningful extent; the majority achieve remission, and—with prophylactic treatment—many patients continue to experience long-lasting full recovery.

References
Major depressive disorder (MDD) is a severe mood disorder affecting individuals of all ages and races characterized by single or recurrent major depressive episodes of at least 2 weeks’ duration, although most episodes last considerably longer. MDD can begin at any age, even in childhood and adolescence, but the mean age of onset of MDD has been estimated around the age of 30, although it can sometimes begin late in life. It has been estimated that 50% to 85% of patients who have an episode will have another episode of major depression. So the question or concern is whether depression is curable.

The prognosis for a single depressive episode that is treated according to standard procedures (involving pharmacotherapy and psychotherapy) is generally good, and most patients return to normal functioning when the episode is over. However, MDD is associated with considerable morbidity and mortality when an initial episode of depression evolves into a recurrent and debilitating chronic illness with significant and pervasive impairments in psychosocial functioning. Studies on the effects of depression on health-related quality of life demonstrate detriments equal to or greater than those for patients with chronic medical illnesses such as ischemic heart disease or diabetes mellitus.

The likelihood of recurrence increases with the number of previous depressive episodes and the severity of the current episode. Patients who already have had three episodes of major depression have a very high risk (about 90%) of having another. Among other risk factors for recurrence of MDD are 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. Asymptomatic recovery from MDD is associated with significant delays in episode relapse and recurrence and a more benign course of illness. Unfortunately, it has become apparent in recent years that the long-term course of unipolar MDD is not only characterized by high rates of recurrence but also dominated by prolonged symptomatic chronicity. In approximately 30% of severely affected or hospitalized depressed patients, residual symptoms and social or occupational impairment persists. It is now well established that about one-third of patients suffering from severe major depression will have a chronic course marked by at least 2 years of illness. According to the new DSM-5, the group of depressive disorders encompasses the following subtypes of chronic depressive illness in adults:

- Major depressive disorder, single or recurrent episode, in partial remission (entitled chronic major depressive disorder in DSM-IV), and
- Persistent depressive disorder (dysthymia) (with an essential feature of depressed mood for more than 2 years).

Individuals suffering from either dysthymia alone or “double depression” (dysthymia plus major depressive episode) have significantly greater impairment in functioning than those with present major depression alone. According to epidemiological and prospective clinical follow-up studies the typical course of MDD involves fluctuating symptoms in which depressive subtypes included in official diagnostic systems do not represent discrete disorders but are stages along a dimensional continuum (spectrum) of symptomatic severity (subthreshold depression). Residual subthreshold symptoms in the course of MDD are associated with a high risk for early episode relapse and a significantly more chronic future course of illness. Due to demographic changes it is of importance that patients with early-onset depression and older adults suffering from an initial depressive episode after the age of 60 appear to be at greater risk for the development of chronicity.

In conclusion, research data and reality in clinical practice teach us that quite a significant proportion of patients suffering from depression do not sufficiently improve over time despite receiving the best currently available treatments. This subgroup of chronically ill patients can be considered not curable (here being "cured" is defined as being permanently free of symptoms of depression) but all our therapeutic and research efforts should be aimed toward an improvement in their psychosocial functioning and quality of life.

References

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“What exposes the psychiatrist so much to discredit and failure as the treatment for melancholy, a syndrome which in many instances is most rebellious to therapy.” (Antonio Vallejo-Najera)

The clinical scope of sadness in humans has been debated for a long time. Following the development of modern psychiatric classifications in 1980, sadness in humans is now recognized as a clinical condition associated with other symptoms and changes in personal functioning, family, and social work, called major depressive disorder. But to consider it as a single entity that comprehends the whole concept of depression is difficult, and this has led to extensive clinical discussion, ranging from the different spectra or the distinction between unipolar/bipolar depression to the expression of anxiety. This heterogeneous clinical picture has prompted research to identify biomarkers and led to the development of diagnostic tests such as the dexamethasone suppression test or the thyroid hormone suppression test. Poor homogeneity, which is linked to the individual variability of human beings, is a major concern in psychiatric diagnoses.

Depression is a worldwide public health problem with a high prevalence rate, and has been identified as the fourth leading medical condition contributing to the global burden of disease. Major depressive disorder is also increasingly recognized as a recurrent and potentially chronic and disabling condition. A large USA study (STAR*D [Sequenced Treatment Alternatives to Relieve Depression]) reported response rates in terms of effectiveness of first treatment close to 40%, while follow-up studies in North America and Switzerland allow us to infer that up to 60% of all patients who suffer from one episode will have subsequent ones and experience a decrement in mental functioning. Each new depressive episode is associated with a renewed risk of future episodes and functional impairment. Each episode seems to increase the likelihood of subsequent recurrences. Published studies suggest that 30% to 50% of patients achieve only partial remission from a depressive episode. Even if there are some risk factors that can help us predict recurrence of the disorder—as such family history of affective disorders, female gender, onset before 25 years, previous recurrence, negative cognitive styles, exposure to stressful life events, absence of social support (especially in women), and comorbidity—they also fail to predict with absolute certainty the recurrence of the disease.

It is likely, therefore, that between 30% and 50% of patients will only experience one episode in their lifetime. For this group of patients, depression is indeed curable. However, this statement is itself problematic, as there are no tests to identify who will recover and who will have to continue struggling with depression chronically or episodically. The concept of remission in the treatment of depressive patients has gained growing attention in the last decade and is now the accepted goal of the acute treatment of depression. With such a limitation, the current approach is based on phased managed intervention, where three phases are generally distinguished: acute management, continuation, and maintenance. Acute management focuses on the use of drug therapy, psychotherapy, electroconvulsive therapy, or a combination of them. The continuation phase aims to consolidate the response obtained and to achieve full symptom remission and relapse prevention, and normally takes between 4 and 6 months. Maintenance is aimed at those patients with three or more episodes of depression or two severe episodes that may need to be maintained on antidepressants for a long-term period or even indefinitely.

Depression is treatable rather than curable. The responsible message to the patient and both the general and the medical community is to emphasize the importance of getting treatment and maintaining it over time as a means to full remission and personal, family, and social recovery.

References
Owing to its different clinical presentations, degrees of severity, comorbidities, treatment responses, and outcomes, depression supports the notion of the “heterogeneity” of various mental disorders. Whether its forms arise as an illness remains a rather complex issue.

The hypothesized multifactorial etiology of depression, according to the “biopsychosocial” model, postulates disruptions at one or more of these spheres, or at different levels within each sphere, in an interactive way that adds to that complexity, as these factors might trigger the depressive illness or change its consequences.

At the biological sphere, the likely factors responsible for genetic, biochemical (within multiple extracellular, membranous, and intracellular stations), neurological, neuroendocrinological, neuroimmunological, and circadian rhythm may underlie depression, prolong its episodes, and alter response to treatment.

Thus, depression could be viewed as many disorders or different facets of the same highly heterogeneous disorder. Successful treatment of depressed subjects should regulate and normalize these underlying factors.

Agomelatine provides a means of resynchronizing the different biochemical and biological rhythms, giving a more valuable therapeutic intervention in managing major depressive disorder (MDD) and anxiety disorders by its direct antagonism of 5HT2c receptors, resulting in a consequent increase in dopaminergic and adrenergic neurotransmitter levels at the frontal cortex and a subsequent decrease in glutamate release and increase in brain-derived neurotrophic factor (BDNF) at the intracellular level. As a consequence, neurogenesis is increased and this effect is augmented by its chronobiotic effect on clock genes, which alleviates depressive symptoms related to the biological clock such as mood, energy, sleep, and appetite.

The extent of these actions incorporating dopamine and noradrenaline preserves emotional reactivity, cognition, and sexual function, combats anhedonia, and causes no discontinuation symptoms. All of this encourages adherence throughout the treatment period, strengthens durable improvement, lessens relapse risk, and helps depressed subjects to reach complete recovery and resume a normal life.

Other antidepressants may also have some effects on some of those parameters. However, their effect is not optimized as in the case of agomelatine, which is overall a positive good step forward on the path to real healing.

There is still considerable controversy regarding improvement in core and specific symptoms of depressive syndrome with antidepressant treatment, sustained response to treatment, and remission because of the limitation that antidepressants do not treat the underpinnings of the disease process. Comorbidities, which are the rule rather than the exception in psychiatry, add to this challenge as well. To appraise the benefits of antidepressant medications, they must be compared with the effects achieved by the most current medical and surgical interventions, and this confirms that they are never curative. Recovery-oriented medical practices that aim for the highest quality of life are still facing many challenges. The drugs currently available offer a glimmer of hope, but a glimmer only: they were developed based on what we know about depression. But what remains to be known is greater still. So “don’t blame the players, blame the game”: it’s not those who design the drugs who are at fault, it’s the premises they have been working on until now. Discovering the antidepressants of the future will require some serious thinking out of the box!

References
Depression is a common mental disorder characterized by the presence of sadness, loss of interest or pleasure, feelings of guilt or worthlessness, disturbed sleep or appetite, tiredness, and lack of concentration. Depression is the most common mood disorder. It is a very common problem, affecting an estimated 350 million people worldwide, and is, according to the World Health Organization, the leading cause of disability worldwide. Some authorities estimate that at least 12% of the adult population has suffered or will suffer from a major depressive episode in the future.

We know that depression is a serious medical illness that affects the brain and involves multiple causes, including genetic, environmental, psychological, and biochemical factors. Moreover, social conditions such as poverty, homelessness, and violence in the community can increase the chances that people become depressed. We also know that there are effective treatments for depression, including the use of antidepressants and psychotherapy—for which there are multiple options to choose from—and that most people get better faster if you use both. But is depression curable?

To establish a diagnosis of major depressive disorder, it is important to confirm the presence of multiple symptoms, each of which is associated with poor information processing in certain brain circuits. Pharmacotherapy should then be aimed at creating an effect on the neurotransmitters that are hypothetically involved—which could be achieved if they generate a single disorder—rather than symptom remission. One of the major unanswered questions about the natural history of the disease regards its progression. In adults experiencing a major depressive episode and responding well to initial treatment with antidepressants, treatment should not be suspended until 9 to 12 months of recovery have elapsed. Treatment—including adherence—must be monitored periodically. The frequency of monitoring should be determined by the compliance and severity of symptoms.

Statistics tell us that one of the features of this disease is a remission rate of approximately 65% with the use of pharmacotherapy and that out of the patients who go into remission a certain percentage will not relapse; this percentage may be increased by including some psychotherapy techniques in the treatment, including interpersonal psychotherapy, cognitive-behavioral, and problem-solving techniques, which have been shown to produce the best results.

The paradigm for the pharmacological treatment of depression has changed in recent years and is currently aiming for complete remission of symptoms and complete maintenance of remission—so that no relapses occur—as the final goal of treatment. This has led to a tendency to use multiple drug mechanisms and commonly using more than one drug, in addition to psychotherapy. However, the symptomatic manifestation of depression remains a very important and largely normative parameter for the choice of antidepressant use among clinicians.

Some of the major challenges facing clinicians who intend to carry out their work rationally, include how to properly master the mechanism of action of the various current drugs of choice and how to master the effective strategies for combining medication and clinical sensitivity to individualize treatment plans. On the other hand, it is unfortunate that around 30% of patients do not adequately take the drug they were prescribed, and that less than half of those who do complete their second month of treatment. So the shocking reality is that only a very small number of patients complete their prescribed treatment properly.

Other complications include the fact that current antidepressants are very effective in relieving symptoms such as depressed mood, suicidal ideation, and psychomotor retardation but are less effective on symptoms such as insomnia, fatigue, lack of interest or motivation and problems of concentration. In addition, response to antidepressants varies depending on the life cycle of patients.

Current evidence from the small number of patients who have achieved remission after a major depressive episode and kept it long term has forced a rethinking of pharmacological treatment schemes, giving preponderance to the goal of achieving remission versus the number of drugs used.

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Statistics tell us that one of the features of this disease is a remission rate of approximately 65% with the use of pharmacotherapy and that out of the patients who go into remission a certain percentage will not relapse; this percentage may be increased by including some psychotherapy techniques in the treatment, including interpersonal psychotherapy, cognitive-behavioral, and problem-solving techniques, which have been shown to produce the best results.
Is depression curable?

As clinicians we can reliably communicate to our patients that we have evidence-based treatments—both psychotherapeutic and psychopharmacological—that overall may improve the prognosis of depression. However, due to the points raised above we may be reluctant to use the term cure for our treatments when introducing them to our patients even if they meet the definition. More precisely, we may instead specify that our treatments are cures simply because they increase the likelihood of a beneficial symptomatic course as compared with no treatment. In trials evaluating drugs for the acute treatment of depression, overall 21%-39% and 42%-70% of moderately to severely depressed patients responded in a placebo arm and in an active arm, respectively. Therefore, the likelihood will be increased roughly by a factor 2. When response (or better, remission) has been reached during drug treatment, we can also inform our patients that the risk of a subsequent re-emergence of depressive symptoms within the first 12 months will increase by a factor 2 if they discontinue the given drug treatment, compared with continuing the treatment, ie, from 18% to 41%. Likewise, the risk of future recurrences, independent of a current episode can seemingly be reduced.

Those patients that have had previous episodes and who, while being treated, experience long-term absence of episodes may be the group of patients that comes closest to having been cured. However, since a vulnerability to depression often remains, these patients need to continue taking the cure.

In conclusion, depression is curable, but unfortunately only a modest proportion of patients may actually feel cured by our treatments.

References

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Antidepressants are considered the cornerstone of depression treatment. However, their efficacy has been a source of debate in recent years. It is sometimes said that their effect is far from matching the criteria for clinical effectiveness or of questionable clinical significance. Sometimes, it is said that they can be useful only in the most severely depressed patients. Most authors agree that estimates of remission fall below 50%. That is, the majority of patients will benefit at most from an attenuation of their symptoms, far from restoring previous functioning. Nevertheless, it is not reasonable to take this data at face value. Methodological limitations of clinical trials and meta-analyses, differences between trials and clinical practice, and results of other areas of medicine must be acknowledged.

Trials in depression have major drawbacks that hinder the detection of antidepressant efficacy. Our classification systems consist of a hodgepodge of different depressive disorders. Inclusion/exclusion criteria facilitate the enrollment of patients that are not representative of clinical practice. Some procedures favor the inclusion of inadequate patients. In fact, the response rates of placebo and antidepressants have been steadily increasing with consequently smaller effect sizes. Increasing the number of patients is a poor strategy, as larger trials inflate the statistical variance, decreasing study power. Failed or negative trials in depression are superior to 50%. Nevertheless, absence of evidence of a difference is not the same as evidence of absence. Moreover, clinical trials are designed to investigate the therapeutic potential of a drug under standardized conditions. They are not able to tell the extent of efficacy of an antidepressant in clinical practice.

Theoretically, meta-analyses provide the best summary of the puzzling potpourri of trials assessing antidepressant efficacy. However, they are undermined by limitations related to the number and quality of individual clinical trials as well as variations in grouping and inclusion criteria. In addition, there is always a risk of flawed analysis and overinterpretation. These problems have brought an unfair pessimism regarding antidepressants. As a recent example of how meta-analyses can lead to equivocal assumptions, a study showing that the efficacy of antidepressants is limited to the most severe cases of depression was not supported by a patient-level data meta-analysis that found antidepressant efficacy to be independent of depression severity. Of course, antidepressants are not ideal drugs. They do not work for every patient and frequently do not alleviate all symptoms. They have side effects, pharmacological interactions, can have negative effects on other diseases, and they pose concerns during pregnancy and breastfeeding. Welcome to the real world of medicine! Most of these criticisms can be applied to clinical trials, meta-analyses, and pharmacological treatments in general medicine. In fact, the effect size of psychiatric drugs, including antidepressants, is in the same range as most general medical pharmacotherapeutics. Efforts to improve efficacy and methodologies are present in all fields. There is no reason to be particularly pessimistic about the treatment of depression.

Another frequently held assumption is that as clinical trials are very standardized, with highly selected populations of depressed patients, their results are far better than the results obtained in real-world settings. This is not necessarily true. From a clinical practice perspective, trials are like tailors who adapt the person rather than the clothing when the clothing does not fit their customer. In routine practice, psychiatrists do not roll dice; they choose what they judge to be the best treatment for a specific person considering the evidence, their expertise, and their patient’s preferences. Psychopharmacological history, type of depression, side effect profiles, and patient preferences are weighted. Dosages and timing are flexible and it is possible to adopt measures to attenuate side effects. In case of insufficient response or poor tolerability, changing the antidepressant, combination, and potentiation are optional methods. In addition, psychotherapeutic interventions should be considered. Taking everything in consideration, in clinical practice it is possible to help a significant number of patients to achieve remission, restoring quality of life and complete functioning.

References
The concept of a cure seems alien to psychiatry and perhaps for some psychiatric disorders, such as neurodegenerative diseases, it is; but is it applicable to depression? It is important to understand that depression per se is not a single entity; it comprises multiple disorders and subtypes, resulting in its myriad presentations. This suggests that some kinds of depression may be the consequence of a disease process. If this is so, then there is a good possibility that we may be able to identify mechanisms, processes, and specific pathways that underpin these forms of depression, and so the idea of a cure for them is quite conceivable.

What would a cure for depression look like? At a molecular level, a cure could involve the replenishment of depleted or damaged proteins and the restoration of key neurochemical processes. At a functional level, a cure could involve reestablishing misfiring neural circuits. Clinically, these changes would ultimately modulate mood, drive, and cognition. But achieving such a cure, even in a subset of depression, requires detailed knowledge of the pathophysiology of established disease. In other words, we need to discover exactly "what is broken" and then know "how to fix it." This kind of insight would also open the door to understanding how and why depression occurs in the first place, which in turn would provide an opportunity for preventing the disease. Hence it is important to investigate the onset of depression and the emergence of clinical symptoms, and also to examine the precursors to the clinical syndrome. In this vein, a recent study of adolescent girls has shown that the antecedents of depression are accompanied by discernible neural changes in the hippocampus and its emotion-processing interconnections. Though this is a step in the right direction, we are still a long way from finding a cure or preventing depression.

Clinically, a paradigm shift is long overdue. In recent years our frame for treatment outcome has moved from response to remission. This has been useful in emphasizing the importance of completely extinguishing the symptoms of depression with treatment, instead of simply achieving a measurable reduction. The next necessary step is to expand our frame further to encompass recovery; from here we can examine relapse and learn how to prevent further episodes of illness and maintain well-being. This is of utmost importance, because "recurrence" defines depressive disorders; indeed, it is the essence of depression. Therefore, in practice, treating depression properly and completely not only requires a thorough cross-sectional appraisal of depressive symptoms and their suitable treatment using antidepressants and psychological strategies, but it also requires a longitudinal perspective that identifies the psychosocial and lifestyle factors that contribute to the maintenance and recurrence of depression, so that these too are adequately addressed.

The eventual aim of treatment is to achieve healthy emotional functioning. However, this does not mean the simple absence of negative emotions: positive emotions also need to be reinstated and engaged fully. The extent to which this is actually possible is unclear. For instance, it may be that depression compromises the brain’s ability to feel positive emotions in a normal healthy manner and that this alteration is irreversible. Furthermore, even with adequate treatment, it is conceivable that medications such as antidepressants restrict “normal” emotional functioning to the extent that full emotional recovery is simply not possible. Depression certainly alters brain structure and function, and it is no surprise that medications can do the same. The key question and concern is whether these changes are everlasting, or whether they can be reversed, or at least, limited. This is an area in urgent need of research and understanding. In the interim, it is important that we understand positive emotions and include these in our appraisal of depression and, in particular, recovery from depression. To this end, we need reliable standardized measures to capture positive feelings and to test these in depressed patients. In this regard, it is worth noting the recent interest in mixed features in depression and bipolar disorder, especially as it is becoming increasingly apparent that a considerable number of patients with depression have latent bipolar disorder and that, when they are depressed, they may also have mixed features that are likely to be overlooked if not targeted specifically. In other words, we will only find what we are looking for if we pose the correct questions. Relying purely on the phenomenology of mood disorders we have perhaps achieved as much as we can in terms of identifying and defining presentations that reflect underlying diseases. If we are to find a cure for depression, we must start to believe that this is a real possibility, and that depression, or at least some of it, can be conquered. ■

Acknowledgments: NHMRC competitive grant funding.

References
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There has been an evolution of opinions concerning recovery in psychiatry following the transition of the paradigm of mental health care from an entirely medical one to a biopsychosocial one that takes into account not only the biological mechanisms of pathology formation, but also all the diversity of the determinants—including personality-environmental determinants—involved in the process. Contemporary conceptions of recovery are based on a dynamic approach that allows the assessment not only of outcomes of some pathological conditions in the form of a reduction or remission of symptoms, but also of the process of recovery per se when a patient is full of life and maintains his/her social functioning despite the presence of symptoms.1,2

Evaluation of recovery in depression is complicated significantly by the fact that the essential manifestations of the pathological process (depressed mood, anhedonia, anxiety, etc) are very closely connected with patients’ social functioning and quality of life. The only possible approach to such a situation is a personalization of diagnosis, therapy, and assessment of the further dynamics of the conditions with a detailed analysis of clinical and psychological components.

From a clinical point of view, the most important indicators of the process of recovery are therapeutic response and remission. Therapeutic response is a predictor of remission and has been shown to fluctuate within the range of 32% to 70% of patients.3 That is why the first antidepressant prescribed induces remission in only 33% of patients, and why after subsequent switches to four other antidepressants during a year, the total proportion of patients having achieved remission is only 67%.4

Problems in achieving remission are largely associated with the multifactorial nature of the neurobiological mechanisms of depression, including interactions between central neurotransmitters and endogenous opioid peptides providing emotional reactions. In addition, one cannot leave out mentioning the importance of motivation and psychological attitude as they both influence many clinical parameters, including onset of remission. This correlation is supported by data showing that in patients with a negative, neutral, or positive psychological attitude onset of remission is achieved in 51%, 56%, and 69% patients, respectively.5

When both biological and sociopsychological influences impact on the resulting recovery, the physician’s strategy and tactics should be fully oriented toward promoting treatment compliance and a therapeutic alliance. This will allow successful implementation of the numerous therapeutic options that contemporary science can offer. Such options include upitation of the dose of antidepressant, switching to another antidepressant of the same class or of a different class, adding a medication (an antidepressant from another class, a neuroleptic drug, or a mood stabilizer), combination with psychotherapy, and using nonpharmacological methods such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), etc.

Taking into account that patients’ main motivations are to recover functioning and the positive mental health (optimism, energy, self-reliance, emotional control) they had before the disease, the choice of primary antidepressant should be based on the therapeutic properties of the medication regarding not only depressive symptoms, but also recovery of the richness and integrity of emotional reactions, cognitive functions, and social functioning.6,7

Finally, the importance of treatment personalization among the numerous factors influencing recovery in depression should be emphasized. This means using innovative medications that take into account the individual characteristics of the patient (clinical, gender, age, etc).

References
before speaking about the curability of depression, it is necessary to understand what we are treating and what is depression. The present-day definitions of depression are far from the scientific model and are usually defined by a purely descriptive (often based on subjective reports) and behavioral approach. This significantly complicates the search for biological markers and pathogenetically substantiated methods of therapy. It also cannot provide a satisfactory prognosis of the disease course or the therapeutic response. Under these conditions it is possible to speak about curability of depression only hypothetically, using futurological notions and terminology.

First of all, we should analyze and try to explain the major causes of the rapid growth of depression in the 21st century. I believe that this is related to certain contradictions with which Man has been faced as a strictly determined biological species that was formed following a long evolutionary process, and the revolutionary technological changes occurring in the noosphere due to human activities. It is uncertain whether Homo sapiens will be able to cope with this global challenge or whether any qualitative leap or “phase transition” of Man’s psychophysiological and adaptational capabilities will take place. The prognosis for the epidemic growth of depression and its treatment is gloomy; however, there is a certain probability of achieving local success with the introduction of new treatment methods for the individual biological variants of depression. Additionally, a higher level of treatment personalization resulting from the progress made by genetic research may yield better results.

Another important question to ask is, “what therapeutic effect are we expecting to achieve?” Relieving the symptoms of depression and treating depression as a chronic disease while attempting to prevent relapses and preserving a high level of social adaptation and quality of life during remission are very different therapeutic tasks. We have become fairly successful at the first task; however, the solution to the second task does not seem to exist at the moment. The notion of recovery in depression should be comprehensive and cover not only complete reduction of the main symptoms, including residual subthreshold symptomatology (ie, achievement of remission), but also continued maintenance during remission, and complete restoration of cognitive, personal, and social functioning with preservation of an acceptable level of quality of life.

Neurotransmitters, chronobiological, neurotrophic (neuroplasticity), and stress-diathesis models of depression have become widely used; however, other mechanisms are also possible. Most mechanisms are described in both neurological and mental diseases; this is not surprising as the different spheres of cerebral activity are closely related to each other and integrated into the holistic system of the human “psyche.” Also, depression is probably not a homogenous disease, and its causes are varied. This heterogeneity is reflected in the modern diagnostic criteria for depression, which so far have been based to a greater extent on a phenomenological (symptomatic) approach than on a nosological (medical) model. This is in particular evidenced by the high comorbidity (up to 50%) of recurrent depression with anxiety disorders, a high placebo effect (up to 50%), and the heterogeneity of the effects of modern antidepressants. Uniting artificially under this diagnosis the fairly different clinical features, course, pathogenesis, and therapy response of conditions such as melancholic, atypical, and psychogenic (reactive) depressions or depressions in which psychomotor retardation, anxiety, anhedonia or psychic anesthesia, and cognitive disorders with depressive ruminations predominate makes the search for the biological basis of these conditions and more effective methods of therapy difficult. Evidently, when the disease develops at a young age, genetic factors and maybe early stress play a significant role. In mature and old age, chronic stress, chronobiological disturbances, and comorbid somatic diseases acquire greater importance. In addition, during the chronic course of depression, cognitive impairment and neurodegenerative changes develop. It is also evident that in most depressive patients sleep is altered and desynchronization of circadian rhythms and of rhythms that have another periodicity is observed, which may be the main pathophysiological link of depression. Although the causal relation between these disturbances and recurrent depression has not yet been established, a chrono-therapeutic strategy should be taken into consideration in the complex therapy of depressive patients since it may provide a higher effectiveness not only in regard to adequate reduction of symptomatology, but also in providing prophylactic effect and in achieving a higher level of social functioning and quality of life.

The absence of a single harmonious theory of depression stimulates our research interest, which in recent years has been aimed at searching for reliable biological markers for the disease and new, more personalized, methods of treatment.
Can depression be cured? May we cure human sadness? Can we speak about a cure when faced with an episodic disorder? Does the beginning of a manic episode represent a cure for depression? These questions may not make sense, but they frequently occur in the minds of clinical psychiatrists, and highlight the difficulty of dealing with such a fuzzy disorder.

Depression has been known since the Old Testament (the story of Job) and was described by Hippocrates. However, it defies clear definition and delimitation. Several authors agree that only the melancholic criteria may be considered as a pathological symptom of depression,¹ but recent discussions about the inclusion of grief reactions in the DSM-5 criteria of major depression point to the difficulty in distinguishing between common human reactions and their pathological developments. Perhaps we are looking at similar phenomena, but from different angles. Can we link these different visions in order to understand the nature of the phenomenon?

From the pathology point of view, the main idea is that depression is a disorder of rhythms.² Melancholic symptoms include early-morning waking, morning worsening of mood, weight loss, and loss of sexual desire. Depression occurs in episodes, with some seasonal incidence. The general picture is a loss of energy and slowing of all motor and cognitive activities. Sometimes, the episode remits spontaneously or switches to an episode of great energy and activity, which is called mania or hypomania. Sleep or light manipulation can modify the course of mood disorders, emphasizing their rhythmic nature.

Rhythms are universal features of life. Every organ, cell, neuron, gene, or body fluid pulses with a known rhythm, and life results from the harmonization of all these rhythms. External or internal events may disturb some rhythms, but homeostatic reactions tend to keep them in line. The diencephalon is the great synchronizer of vertebrate rhythms. Brain scars or genetic dysfunction of ionic channels (present in epilepsy and bipolar disorders)³ may desynchronize some neuronal rhythms. Thus, the thalamus recruits and distributes the neuronal impulses, producing a seizure and resynchronizing them. Hormonal rhythms are also regulated in the hypothalamus and pituitary gland. Furthermore, the diencephalon extends causally to the pineal gland, another gland that produces melatonin in response to environmental light, thereby regulating the circadian rhythms.

However, in mammals, the hypothalamic suprachiasmatic nucleus takes over from the pineal gland as a circadian pacemaker. Mammals live in families, sometimes displaying nocturnal activity, and they need to be synchronized with each other more so than with the sun. Personal relationships imply a synchronization of activities and, even more, of physiological rhythms. When we lose a close person, we also lose an important source of synchronization and feel empty. Some complex feelings can then lead us to avoid other people and refuse other attachments and synchronizations. Furthermore, we can become desynchronized with the sun and all our rhythms may be disturbed.

Loss (of people, roles, and expectations)⁴ is a factor in depression, and mourning can be its model.⁵ Some authors also point to romantic passion as a model of mania.⁶ Passionate and manic people are very energetic, optimistic, and persuasive. In fact, passionate people try to synchronize with the person(s) they love, thus “rebuilding” what they have lost. Manic patients do so spontaneously.

So, should we cure depression? Yes and no. Life is made of changes where something is lost and something is gained. We may treat depression if patients are not able to regain something when they experience loss, if intense reactions, bad feelings, or previous conditioning lead them to add further losses to the original loss, and when these episodes are mere repetitions without sense. In every other circumstance, people should be allowed to grieve and to fall in love.

References
Maj or depressive disorder (MDD) is characterized by a combination of symptoms that interfere with a person’s ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Major depression is disabling and prevents a person from functioning normally. According to this definition, we can consider recovery as a return to previous global functioning. Classically, recovery is defined by the persistence of complete remission for a period of 4 to 6 months. However, studies have found that about one-third (34% and 32%, respectively)1,2 of patients recover from previous global functioning. Classically, recovery is defined by the persistence of complete remission for a period of 4 to 6 months. However, studies have found that about one-third (34% and 32%, respectively)1,2 of patients recover from major depressive episodes (MDEs) with residual subthreshold depressive symptoms (SSDs).

Judd et al have shown that residual SSD recovery is associated with very rapid episode relapse, which supports the idea that SSD is an active state of illness.2 Moreover, residual SSD recovery has a significantly stronger association with early depressive episode relapse than the recurrent MDE risk factor (OR, 3.65 vs 1.64, respectively). Asymptomatic recovery is associated with a prolonged delay in episode recurrence.

Over 80% of patients who have had a first episode will experience another one during their life. Consequently, unipolar depressive disorders are considered to be recurrent disorders. Kendler et al found strong evidence that the strength of the association between stressful life events and onset of depression declines with increasing number of previous depressive episodes, which supports the kindling hypothesis.3 These models predict that with recurrent episodes of major depression, the role of environmental stressors will progressively diminish. According to these models, each episode of depression leaves a “scar” that makes the subject more vulnerable to the onset of a new episode, and therefore a trigger of a lesser intensity is required to give rise to each event. In 1999, Sheline first exposed the notion of neurocognitive scars induced by the neurotoxicity of depressive episodes, by showing a correlation between the degree of hippocampal volume reduction and the total duration of a major depressive episode.4 Gorwood et al assessed the impact of depression on hippocampal function; their findings suggest that the intensity of past depression contributes to the impairment of memory performance when patients have recovered.5 Consequently, there may be advantages in early treatment, maintained for a sufficient period, and in not tolerating chronicity or even partial remission. Residual SSD is a treatment target to prevent a relapse. In a 3-year prospective study of 267 patients with MDD, Conradi et al found that on average three individualsymptoms (cognitive problems, lack of energy, and sleep problems) dominated the course of depression and were present 85% to 94% of the time during depressive episodes and persisted in 39% to 44% of remitted patients.6 Clinicians also need to distinguish persisting residual symptoms, newly emerging or re-emerging symptoms, and late-onset antidepressant side effects. Some patients with major depression report experiencing a narrow range of emotions, which may appear as a side effect of antidepressants. This phenomenon—also known as emotional blunting—can represent residual symptoms of depression or side effects of antidepressant treatment. C. J. Harmer has shown that treatment with selective serotonin reuptake inhibitors (SSRIs) can curb the neural processing of rewarding stimuli, an effect that may underlie the questioned effectiveness of SSRIs in depressive conditions characterized by decreased motivation and anhedonia, and could account for the experience of emotional blunting reported during SSRI treatment.7

Growing evidence suggests that some MDD symptoms (fatigue, cognitive symptoms, lack of motivation) may not respond to the conventional treatments that are effective in treating other core MDD symptoms. Early identification of these symptoms, combined with new treatment approaches, may restore optimal global functioning in our patients.

**References**


For the past two decades, researchers have been trying to better understand the nature of major depressive disorder in the hope that this deeper understanding will help those affected by the disease. Major depressive disorder, once manifested in a patient, inevitably not only affects the patient, but also the patient’s family and social circles. Naturally, these unfortunate victims desire an answer to the question: is depression curable?

The answer to this short and emotional question is surprisingly difficult to obtain. To be able to answer the question, one must look at information from research and from extensive clinical observations, both in the past and in the foreseeable future.

A key characteristic of major depressive disorder is the recurrence of episodic attacks. In 1989, the MacArthur Foundation launched an initiative to summarize and document the outcomes of this disease; and in 2006, the American College of Neuropsychopharmacology (ACNP) refined the criteria for remission to assist subsequent clinical studies. The result is an extensive documentation on five major areas: response, remission, recovery, relapse, and recurrence. The curability of depression then boils down to treating individual episodic attacks and lengthening the recovery periods between attacks. This implies that the process responsible for the ongoing episode has, at least, been arrested even though the underlying mechanism responsible for the recurrence may or may not be eradicated yet. However, if the ideal is to maintain the length of the recovery phase for as long as possible, we must understand what causes recurrences as well as what helps prevent recurrences. Evidence from previous studies strongly indicates that before a patient can be in recovery, the patient must first attain full remission, because one of the leading causes of recurrence is partial, or incomplete, remission. Exhibiting residual symptoms is a stronger factor in predicting chances of relapse than the severity of the condition and the number of previous depressive episodes. Studies have also shown that going into remission has a stronger positive impact on functioning, prognosis, and the maintenance of a stable enduring state than achieving a response. If the immediate goal for treating depression is for the patients to go into remission, a good benchmark is the remission rate. Efficacy studies in the past 10-20 years have shown a trend toward better and faster remission in patients treated with newer antidepressants relying on broad-spectrum mechanisms compared with patients taking older antidepressants. These new antidepressants, therefore, will potentially increase the remission rate. Another way to increase the remission rate is to eliminate factors that prevent patients from going into remission, for example, discontinuation of treatment due to adverse effects.

Aside from its severe mental toll, major depressive disorder can also lead to disabilities and is predicted to be the leading cause of disabilities worldwide by 2020. Fortunately, although patients are critically affected in their daily functions by depression, studies have shown that successful curing of the disease leads to a significant decrease in impairment in psychosocial functioning. Restoration of the patients’ global functioning will directly follow from the successful treatment of the disorder. The less affected the patients are by the episode, the more they can resume their previous level of functioning.

So, is depression curable? As of now, there is no clear answer to this question. However, with advances in different forms of treatments, organized research, and a clear goal for treatment, we will be able to further the understanding of the nature of this disease and its treatment. This will ultimately help us refine and improve our answer in the future.

References
Depression is a common mental disorder, characterized by low mood and diminished interest or pleasure. Currently, the main medical treatment for depression is antidepressant medication. Is depression curable?

Recovery is defined as a full remission with no symptoms for a certain length of time. However, many depressed patients fail to achieve remission after being placed on initial therapy with an antidepressant. In the STAR*D study (Sequenced Treatment Alternatives to Relieve Depression), which included non-psychotic major depressive disorder outpatients, it was found that even with systematic measurement-based treatment, only approximately one-third of patients reached full remission after one treatment step, with two-thirds reaching remission after four treatment steps. This study clearly demonstrated that a large portion of depressed patients cannot achieve remission or recovery with initial antidepressant treatment. However, part of these nonremitted patients can achieve remission with other antidepressants.

Failure of depressed patients to achieve remission represents a major public health concern. Inadequately treated depression is associated with poorer quality of life, deleterious personal and societal economic ramifications, and increased mortality rates. Some of the primary challenges for the treatment of major depression are (i) how to increase the remission rate, and (ii) whether it is possible to subgroup depressed patients based on biological markers or clinical characteristics before treatment to predict remission rates.

How can we increase the remission rate? Even when an antidepressant is effective, lack of compliance can be a major problem in the treatment of depression. The ability of the depressed patient to tolerate a drug’s adverse effects greatly influences his or her treatment compliance, as well as the probability of relapse. For depressed patients who do not respond to initial antidepressant treatment, the next pharmacological treatment options include switching to another antidepressant with a different mechanism of action or augmenting the initial therapy with a second agent. Developing novel antidepressants with new therapeutic mechanisms and fewer adverse effects could improve adherence and increase remission rates. In addition to pharmacotherapy, psychotherapy shows promise in enhancing remission rates. It has been shown that the combination of pharmacotherapy and short-term psychotherapy is significantly more efficacious than either pharmacotherapy or psychotherapy alone. Various nonpharmacological, neuromodulatory strategies, such as electroconvulsive therapy (ECT), magnetic seizure therapy (MST), repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and deep brain stimulation (DBS) have been used to treat treatment-resistant depressed patients.

Can we group depressed patients into subgroups based on biological markers or clinical characteristics at baseline to predict remission rates? Studies on this topic are still in the initial stages. A recent study suggested that using baseline evaluations of patients’ anguish/restlessness, reduced emotional reactivity, reduced attention, reduced motor response, feelings of worthlessness, and mood characteristics items, it was possible to correctly classify 88% of the sample group as remitters or nonremitters with a sensitivity of 0.77 and a specificity of 0.96. Other studies using neuroimaging, electroencephalograms, or genetic analysis have suggested that there are some biological biomarkers of remission in major depression patients, but these need further confirmation from replication studies.

References
17. M. Yeghiyan, Armenia

In most societies the word depression has a colloquial connotation meaning “bad mood.” Mood variations throughout the day are within the norm and are an indicator of mental health rather than disturbance. A healthy person may experience daily combinations of different emotions such as joy, satisfaction, or irritation, which may contribute to having a bad or a good day and may provide the feeling of having “a zest for life.” In medical terms, depression is a disease that can disrupt the emotional balance for a prolonged period of time and significantly debilitate a person.

Depression may occur as a result of a previous traumatic event, but often there are no apparent external triggers. In terms of the clinical picture, depression disrupts the plasticity, the dynamism, as well as the integrity of all emotional processes, and ultimately leads to a complete physical and mental collapse. Biologically the picture is vague; however, it is quite clear now that depression is an imbalance between receptors and neuromediators in brain tissue. Thus, the target organ is the brain itself.

The biggest improvement for the treatment of depression is the discovery of antidepressant medicine in the last century. There are continued efforts to develop new and improved antidepressant medications. With each new drug there are new hopes and new perspectives, and sometimes disappointments. However, advances in psychopharmacology have led to the development of various hypotheses on the pathogenesis of depressive disorders. Until the late 20th century the monoamine hypothesis was widely recognized as the fundamental cause of affective disorders. This hypothesis determined the development of the following types of antidepressants:

◆ Tricyclic antidepressants with nonspecific effects on multiple receptor system
◆ Selective single-action antidepressants (eg, SSRIs, SNRIs)
◆ Multiple selective-action antidepressants (SSNRIs)

Over time, these drugs have become the standard in the treatment of depression; however, these treatments have numerous side effects such as sexual dysfunction, apathy, and changes in behavior and appetite. In my practice, patients treated with the standard SSNRIs/SNRIs approach generally rated their condition as good but often noted a sense of “artificiality” (feeling robot-like) and a decrease in the intensity of their feelings. The 21st century brought about other therapeutic targets for depressive disorders beyond the monoamine hypothesis. This was due primarily to the inconsistency of the monoamine hypothesis and the empirical data on the efficacy of other treatments such as electroconvulsive therapy, phototherapy, and sleep deprivation.

The more immediate amelioration of depressive symptoms with electroconvulsive therapy or sleep deprivation provides an attractive alternative to the delayed onset of therapeutic action of monoamine antidepressants. There are also considerations regarding the cognitive components of depression and the role of glutamate and γ-aminobutyric acid (GABA) in neuroplasticity. The search for novel therapeutic agents continues. Currently, new therapeutic treatments in the pipeline include ketamine, a N-methyl-D-aspartate receptor antagonist, microRNAs, an entirely new class of therapeutic agent that mood stabilizers use as downstream effectors, circuitry-based targets such as deep brain stimulation, vagus nerve stimulation, and magnetic stimulation. Another therapeutic target is inhibition of melatonin in the pineal gland, which causes a change in the concentration of cortisol and adrenocorticotropic hormone (ACTH) and regulates the balance of catecholamine synthesis, which in turn “resets” the circadian rhythm. This modality is by far the most reasonable since it mimics the natural mechanisms of mood regulation unlike monoaminergic antidepressants.

The answer to the controversial question of whether depressive disorders can be cured depends on the treatment goals chosen by physicians. Common sense, however, tells us that a physician should not focus solely on symptomatic targets, but rather on the restoration of the patient’s optimal global functioning. In other words, a person should not be free of “sadness” but truly happy, and experience the full range of feelings and social functioning that defines a healthy person. Such targets should include removal of symptoms of depressive disorders and restore to health the parts of human mental health that have been affected by the disease. ■

References
Valdoxan has been shown to possess short- and long-term antidepressant activity in clinical trials vs placebo and vs selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). This antidepressant activity was confirmed in daily clinical practice... Valdoxan improves the core symptoms of depression, resulting in an early improvement in emotional processing. This can lead to an improvement in functioning and, therefore, complete recovery.

Valdoxan: recovering usual functioning in depressed patients

by C. Muñoz, France

It is now widely recognized that improvement in global functioning should be part of the treatment of depression. In order to achieve this improvement, novel treatment strategies are needed in our therapeutic armamentarium. Valdoxan is precisely such a strategy for the treatment of depression due to its unique mode of action (synergy between melatonergic receptor agonism and 5HT2C receptor antagonism). In this article, the antidepressant efficacy of Valdoxan is described, from symptomatic improvement to early and sustained improvement in functioning. The efficacy of Valdoxan in moderately to severely depressed patients has been confirmed by a new placebo-controlled study as well as in a meta-analysis of short- and long-term studies versus SSRIs/SNRI. Valdoxan has also demonstrated early efficacy in restoring pleasure, interest, and positive emotions in depressive patients. These effects result in early and sustained improvement in functioning, which was observed in several clinical trials and clinical practice. Valdoxan is thus established as the only antidepressant to promptly act on these major aspects of depression, thereby demonstrating that Valdoxan possesses a comprehensive antidepressant efficacy.

Medicographia. 2014;36:501-507 (see French abstract on page 507)

It is widely recognized that major depression remains undertreated in spite of the efforts made to understand its pathophysiology and the treatments currently available to patients. This disabling disease induces significant impairments in important areas of functioning; major depressive disorder actually exerts a significant negative impact on overall functioning and quality of life (ie, employment status, stability of interpersonal relationships, financial success) and is associated with one of the highest number of days out of role at the societal level of any physical or mental disorder.1

The efficacy of antidepressants in major depressive disorder has long been assessed only by measuring symptom reduction. However, it is now being recognized that to consider remission only as a reduction in depressive symptoms is not enough since clinical remission is not necessarily accompanied by optimum functioning. A recent study conducted in 274 depressed outpatients,2 about half of whom were considered to be in remission, revealed that these patients did not feel that they were actually free from depression. Residual symptoms and cognitive dysfunction are among the remaining symptoms that were thought to induce this subjective impression.
From the patients’ perspective, remission starts with a return to positive mental health, followed by a feeling of returning to their usual normal self, a return to a usual level of functioning at work or home, feeling in emotional control, enjoying family and social relationships, and only at the bottom of the list comes the absence of symptoms of depression.\(^5\) Recovering emotions is essential to improving the functional outcome in depressive patients. Significant functional impairment, if not adequately treated, may precipitate relapses and recurrences.\(^4\)

It is, therefore, increasingly recognized nowadays that the treatment of depression not only needs to achieve statistical remission—as measured by classical depression scales such as the Montgomery and Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), and Quick Inventory of Depressive Symptomatology (QIDS)—but also needs to be effective in clinical practice. To bring about a full recovery, an antidepressant needs to provide a global improvement in functioning. It is thus essential that the functional impairments associated with depression are monitored and assessed regularly, and treatments should be developed to treat them, maybe even with the use of novel strategies.\(^5\) The current trend is to consider functioning as a critical target for therapeutics.\(^8\)

Functional assessments can be performed with validated tools such as scales and questionnaires filled by patients; among them, the most widely known and used is the Sheehan Disability Scale (SDS),\(^2\) a ten-point visual analog scale used by patients to auto-evaluate the disruption of their work/school, social life, and family life/home responsibilities. Other aspects of functioning can be evaluated by the Social Adjustment Scale-Self Report (SAS-SR)\(^8\) or by the clinician-rated Global Assessment of Functioning scale (GAF scale).\(^9\) Residual symptoms associated with functional impairment such as daytime sleepiness, impairment in sexual function, somatic complaints, and cognitive impairment, are also assessed by specific scales.\(^5\)

A good way to informally assess psychosocial function recovery in daily practice is to ask patients at each visit a few specific questions targeting aspects such as absenteeism, level of enjoyment regarding their interactions with others, or favorite activities or interests.

As mentioned above, treatments that improve functional outcomes in depression may need to use novel strategies or novel therapeutic targets. Valdoxan is a recent antidepressant drug with a novel pharmacological profile: it is both a MT\(_1\) and MT\(_2\) receptor agonist and a 5HT\(_{2C}\) receptor antagonist, and the synergy between both properties is responsible for the antidepressant efficacy of Valdoxan. Valdoxan has been shown to possess short- and long-term antidepressant activity in clinical trials vs placebo and vs selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs).\(^10-12\) This antidepressant activity was confirmed in daily clinical practice.\(^13,14\) As discussed previously, Valdoxan improves the core symptoms of depression, resulting in an early improvement in emotional processing.\(^15\) This can lead to an improvement in functioning and, therefore, complete recovery. This is what makes Valdoxan different from conventional antidepressants. In this article, the antidepressant efficacy of Valdoxan will be reviewed in light of its early and sustained improvement in functioning.

**Valdoxan: from symptomatic improvement to improvement in functioning**

The antidepressant efficacy of Valdoxan has been evaluated in 12 short-term studies versus placebo, 7 of which had a positive outcome, 3 of which failed, and 2 of which were negative. In all positive placebo-controlled trials, efficacy was shown in severely depressed patients. A total of 7 trials were completed in which Valdoxan was compared directly with SSRIs/SNRIs; Valdoxan was shown to be superior in 2 trials, and non-inferior to its comparators in 4 trials. Long-term trials have also demonstrated the antidepressant efficacy of Valdoxan versus placebo and SSRIs.

One of these studies deserves special attention since it clearly confirmed the antidepressant efficacy of Valdoxan in moderately to severely depressed patients. This study was a dose-regimen study where Valdoxan was administered to moderately to severely depressed adult patients (HAM-D ≥ 22) at fixed doses of 10 mg or 25 mg, or at a flexible dose of 25-50 mg for up to 6 weeks with the possibility of extending the treatment to 24 weeks. After 6 weeks, the decrease in HAM-D score and the percentage of responders were shown to be significantly in favor of Valdoxan for each of the dose regimens (P＜0.001 for the 10 mg group and P＜0.0001 for both the 25 mg or 25-50 mg groups).\(^16\) In the subgroup of more severely depressed patients (defined as having a HAM-D score ≥ 25 and a Clinical Global Impression scale (CGI) score ≥ 5 at inclusion), the differences with placebo only reached statistical significance for the 25 mg and 25-50 mg doses of Valdoxan in terms of

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
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<tr>
<td>CGI</td>
<td>Clinical Global Impression (scale)</td>
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<tr>
<td>DLPC</td>
<td>dorsolateral prefrontal cortex</td>
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<tr>
<td>GAF</td>
<td>Global Assessment of Functioning (scale)</td>
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<tr>
<td>HAM-D</td>
<td>Hamilton Depression Rating (scale)</td>
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<tr>
<td>MADRS</td>
<td>Montgomery and Asberg Depression Rating Scale</td>
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<td>QIDS</td>
<td>Quick Inventory of Depressive Symptomatology</td>
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<tr>
<td>RDS</td>
<td>[Widlocher] Retardation Depressive Scale</td>
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<tr>
<td>SDS</td>
<td>Sheehan Disability Scale</td>
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<tr>
<td>SNRI</td>
<td>serotonin–norepinephrine reuptake inhibitor</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>VALID</td>
<td>VALdoxan In Depression (study)</td>
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<tr>
<td>VLPC</td>
<td>ventrolateral prefrontal cortex</td>
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Restoration of pleasure and interest and fewer discontinuations due to adverse events were observed with Valdoxan than with SSRIs. These short- and long-term effects were also greater among patients treated with Valdoxan over 6 weeks. The specific Multidimension-
al Assessment of Thymic States scale (MATHyS) was used to evaluate emotions. MATHyS is a visual analogue scale that rates 7 emotions (sadness, anxiety, panic, irritability, anger, joy, and exaltation) and 5 dimensions (emotional reactivity, cognitive speed, motivation, psychomotor function, and sensory perception). After only 2 weeks of treatment sadness, anxiety, panic, irritability, and anger decreased significantly while joy increased and exaltation remained stable. Valdoxan also induced an improvement in all the dimensions of the scale, motivation being the most improved after 2 weeks of treatment, resulting in a global score that was significantly ($P<0.001$) greater compared with baseline (Figure 3). These changes were correlated with significant decreases in the QIDS and CGI scales after 2 and 6 weeks of treatment. 23

Valdoxan: early and sustained improvement in functioning

Improvement in functioning is the ultimate goal of antidepressant treatment. The efficacy of Valdoxan measured using the conventional scales of depression, the restoration of pleasure, and its specific impact on emotional processing translate into an increase in daily functioning (both social and cognitive). The effect of Valdoxan on social and cognitive functioning was evaluated using specific scales in clinical trials as well as in large studies in clinical practice.

Valdoxan improves social functioning in patients with moderate-to-severe depression

The dose-regimen study mentioned above evaluated social functioning using the Sheehan Disability Scale after administration of Valdoxan for 6 weeks. In adult patients, the doses of 25 mg or 25-50 mg of Valdoxan significantly improved ($P<0.0001$) the three dimensions of the scale—namely, work, social life, and family life. This translated into a significant decrease in the number of days lost ($P=0.046$ and $P<0.001$ for the doses of 25 mg and 25-50 mg, respectively) and in the number of unproductive days ($P<0.001$ and $P<0.0001$ for the doses of 25 mg and 25-50 mg, respectively) in comparison with placebo (Figure 4). 16

Figure 3. Evolution of the 5 dimensions of the MATHyS scale in depressed patients treated with Valdoxan for 6 weeks


Figure 4. Improvement in working functional outcomes after 6 weeks of treatment with Valdoxan as evaluated by number of days lost and number of unproductive days.

In clinical practice, three main studies have shown an improvement in functioning with Valdoxan: VALID (Valdoxan In Depression), DIAPASON, and DAVANTAGE.

The VALID study, which included 111 depressed patients treated with Valdoxan, showed a significant improvement in depression—as measured by the MADRS scale—from the first week of treatment (decrease from baseline from 28.7 to 24.8, \( P<0.001 \)) and this significant improvement continued over the 8 weeks of treatment, with a remission rate of 46.8%. CGI scores also showed a positive change: the mean CGI-S score improved as early as the first week of treatment and over the 8 weeks of the study (final score 2.2, \( P<0.001 \)). In parallel, an improvement in functioning was noticed in the three dimensions of the patient-rated SDS scale (where the mean scores decreased from baseline to week 8 of treatment, with a significant decrease achieved as early as week one, \( P<0.001 \)) and the physician-rated scale GAF. The mean GAF scores increased significantly (\( P<0.001 \)) from the second week of treatment (first measurement) up to week 8 (from 60.5 at baseline to 80.2).

The DIAPASON study included more than 3000 depressed patients who were administered Valdoxan and followed up during a period of 6 to 8 weeks. The QIDS and SDS scores evaluated at inclusion and at the end of treatment showed a significant improvement.

The DAVANTAGE study was performed in more than 2000 depressed patients with relatively severe depression at baseline, as assessed by the clinician’s rating of the QIDS and CGI-S scales at inclusion (scores of 16.1 and 4.8, respectively). Assessment of functioning was performed using the Widlocher Retardation Depressive Scale (RDS)—which evaluates different aspects of mental and motor retardation—and the SDS scale. The improvement in QIDS and CGI scores was progressive and statistically significant (\( P<0.001 \)) over the treatment period. Functioning was significantly improved with a decrease in RDS score from 26.6 at inclusion to 11.4 at week 6/8 (\( P<0.001 \)). There was also a significant improvement in the three dimensions (work, social life, family life) of the SDS score, with a decrease in total SDS score from 20.3 at inclusion to 10.2 (\( P<0.001 \)) after 6/8 weeks of treatment with Valdoxan.

◆ Valdoxan improves cognitive functioning
Clinical studies using visual analog scales have shown that Valdoxan provides significant and early improvement in one of the main aspects of cognition—clear thinking—while escitalopram does not.

In clinical practice, the observational DAVANTAGE study, which included 508 patients, used the d2 test of attention, a graphic test designed to assess selective and sustained attention by measuring accuracy, performance consistency, and number of mistakes. The different components of the test include the KL score (concentration performance index: accuracy, number of correct responses minus number of incorrect responses) and the GZ score (quantitative performance index: productivity, number of analyzed items). After 6 to 8 weeks of treatment with Valdoxan, both indexes increased: the concentration performance index changed from 105.7 to 132.8 (\( P<0.001 \)) and the quantitative performance index from 318.1 to 381 (\( P<0.001 \)). Furthermore, the improvement in clinical retardation observed with the RDS test was directly correlated with an improvement in cognition.

The tolerability of Valdoxan was good in clinical trials and observational studies. However, it should be mentioned that cases of liver injury including increases in transaminase levels and, in patients with hepatic risk factors, rare cases of hepatic failure with fatal outcome or liver transplantation have been reported. Therefore, as described in Valdoxan’s Summary of Product Characteristics, Valdoxan is contraindicated in patients with hepatic impairment or transaminase levels exceeding 3 times the normal upper limit and caution should be exercised when prescribing Valdoxan for patients with hepatic injury risk factors. Liver function tests should be performed in all patients and the recommendations of the SmPC should be followed.

Conclusion
The results of the studies described in this article confirm that the dose of 25 mg is the optimal daily dose for Valdoxan. The difference in effect between treatment with Valdoxan and placebo shown in the dose-regimen study is—by far—much greater than what is recommended in the guidelines for short- and long-term treatment and definitely confirms the antidepressant efficacy of Valdoxan in patients with moderate-to-severe depression. What doctors look for first in an antidepressant is that it should have an effect on depressed mood and anxiety, and Valdoxan clearly fulfills this need. But Valdoxan has been shown to go beyond this efficacy and this is what makes it unique among all available antidepressants. What depressed patients expect from an antidepressant is that it will help them get their lives back to normal, ie, to recover the positive aspects of their lives that were lost due to depression, to recover interest and pleasure, to be able to get back to their job, family, and social activities. Valdoxan can give them these positive emotions early in the treatment course.

Valdoxan improves anhedonia, the second core symptom of depression, which is usually addressed by antidepressants only late in the treatment course. Valdoxan’s effect on functioning translates into a decrease in the number of lost and unproductive days. This effect, together with the improvement in social and cognitive functioning found in a large number of patients in clinical practice, confirms the benefits of treatment with Valdoxan. The correlation between improvement in retardation...
and improvement in cognition shown in the DAVANTAGE study is extremely important since improved retardation plays a major role in functional remission, even when clinical remission is observed.

Brain imaging has shown that these improvements have neurological correlates. From the very first week of treatment, Valdoxan acts on those areas of the brain that are implicated in the process of anhedonia and automatic regulation of emotions (VLPC and amygdala). Then, after 7 weeks of treatment, Valdoxan prepares the brain for further normalizations in the activity of the structures implicated in cognitive control and motivation.

In summary, the results presented in this article establish Valdoxan as the only antidepressant with early efficacy on the major symptoms of depression, such as loss of pleasure and interest and loss of motivation. Thus, Valdoxan’s comprehensive antidepressant efficacy answers the needs of both doctors and patients for a more complete recovery.

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**Key references**

24. Light SN, Heiler AS, Johnstone T, et al. Reduced right ventrolateral prefrontal cortex activity while inhibiting positive affect is associated with improvement inhedonic capacity after 8 weeks of antidepressant treatment in major depressive disorder. Biol Psychiatry. 2011;70:962-968.
Il est maintenant largement reconnu que l’amélioration du fonctionnement général doit faire partie du traitement de la dépression. À cette fin, notre arsenal thérapeutique doit s’enrichir de nouvelles stratégies. Valdoxan représente une approche novatrice dans le traitement de la dépression du fait de son mode d’action unique (synergie entre agonisme des récepteurs mélatoninergiques et antagonisme des récepteurs 5HT2C). Cet article décrit l’efficacité antidépressive de Valdoxan, qui s’étend de l’amélioration des symptômes jusqu’à l’amélioration fonctionnelle précoce et prolongée. Une nouvelle étude contrôlée contre placebo et une métaanalyse d’études à court et à long termes versus ISRS et IRSN ont confirmé l’efficacité de Valdoxan dans la dépression chez des patients modérément à sévèrement déprimés. Valdoxan est aussi efficace de façon précoce en restaurant le plaisir, l’intérêt et les émotions positives chez les patients dépressifs. Ces effets entraînent une amélioration fonctionnelle précoce et prolongée observée dans plusieurs études cliniques et en pratique clinique. Valdoxan est ainsi le seul antidépresseur capable d’agir rapidement sur ces aspects majeurs de la dépression, preuve de son efficacité antidépressive complète.
A valid diagnosis is distinctly more likely to promote remission as it will shape the choice of the most appropriate treatment modality and the way in which it should be applied, whether sequentially (eg, initially prioritizing the patient’s melancholic depression by medication and then addressing his/her alcoholism with a specific program) or pluralistically (eg, if multiple modalities are used such as antidepressant medication and psychotherapy, how are they best assembled and combined?).

Remission has somewhat varying meanings and operational definitions to the patient, the clinician, and the researcher. In response to five questions put by the interviewer the author responds by offering a clinical perspective. Such a clinical approach weights the importance of diagnosis and a formulation—particularly in identifying the particular depressive subtype and likely causes—as both should shape, if not dictate, the prioritized treatment modality and management nuances. If remission does not occur, then revisiting the diagnosis and considering which factors may be inhibiting progress is the next logical step.

Remission has somewhat varying meanings and operational definitions to the patient, the clinician, and the researcher. In response to five questions put by the interviewer the author responds by offering a clinical perspective. Such a clinical approach weights the importance of diagnosis and a formulation—particularly in identifying the particular depressive subtype and likely causes—as both should shape, if not dictate, the prioritized treatment modality and management nuances. If remission does not occur, then revisiting the diagnosis and considering which factors may be inhibiting progress is the next logical step.

Toward full remission: improvement in functional outcomes in depression

Interview with G. Parker, Australia

Remission has somewhat varying meanings and operational definitions to the patient, the clinician, and the researcher. In response to five questions put by the interviewer the author responds by offering a clinical perspective. Such a clinical approach weights the importance of diagnosis and a formulation—particularly in identifying the particular depressive subtype and likely causes—as both should shape, if not dictate, the prioritized treatment modality and management nuances. If remission does not occur, then revisiting the diagnosis and considering which factors may be inhibiting progress is the next logical step.

What clinical symptoms are clinically useful to evaluate functional remission in patients?

When judging remission as a clinician, not as a researcher, I tend to favor constructs rather than individual symptoms. Inviting the patients to judge their overall level of mood improvement in percentage terms is a useful initial probe question that most patients readily understand. There are no firm markers but I would expect a patient who had recovered from depression to report being “100% better” without caveats or, when questioned further, to note only minimal issues (ignoring any medication side effects for the moment). A second broad construct is the patient’s level of impairment in getting to work, functioning at work, and/or in addressing daily tasks. I would expect those who have experienced a remission to nominate no distinctive impairment. A third construct is how the patient enters the consulting room and interacts with the clinician—and thus weights “signs” rather than symptoms. Patients whose depression has remitted are likely to present with light in their eyes, a spring in their step, and be more likely to ask how the doctor’s week is proceeding. In essence, “lighter” and able to see beyond their own depression.

If the patient reports full remission it is generally necessary to seek further clarification. The depressed individuals who state that their depression has gone and say “I have my life back” are usually reporting a complete remission. The patient who states “It’s a miracle... I’m no longer depressed at all... you are a magician doctor” could have moved beyond depression remission to a hypomanic state. Such patients should be screened for a medication-induced hypomanic episode or for a previously undeclared or unidentified bipolar disorder.

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I then favor reviewing the depressive features nominated by the patient as most distinctive or distressing when they were initially assessed. This tends to be more useful than assessing all theoretical or manual-listed depressive symptoms and allows the status of all initially distinctive symptoms to be investigated. Moving from a global assessment where remission may be suggested to a review of specific symptoms may identify some symptoms as present—be they residual symptoms or medication side-effects—and both allow improvement to be quantified more finely and the need for any management changes.

Some depressive symptoms indicating less than full remission show some specificity to the depressive subtype. For example, those with melancholia are likely to report that, while improved, early morning anergia and diurnal variation are still present to some degree, and here the consequence of so identifying any residual symptoms is to consider the need for changes in medications or dose regimens.

**How long does it take to achieve functional remission?**

As long as a piece of string is the flip response that comes to mind. Those who remit fully may report so responding in a day, while others report days to years. Different types of depression, as well as different treatments, influence the speed of response.

As recently reviewed,¹ we view melancholia as a “biological” depressive “disease,” showing a low placebo response rate (in the order of 10%) and a preferential response to physical treatments compared with a psychotherapy. In clinical practice, I find broader-action medications (eg, tricyclics, monoamine oxidase inhibitors) to be more effective and with a faster remission onset than narrow-action medications such as selective serotonin reuptake inhibitors (SSRIs), which generally require weeks or, occasionally, months before they possibly induce remission of a melancholic depressive episode. The multiple available medication augmentation strategies (as reviewed by Narasimhan and Kannaday²) are generally positioned as relevant to major depression per se. By contrast, we position them as being specifically relevant only to the “biological” depressive conditions (ie, melancholic and psychotic depression). We have employed several antidepressant augmentation strategies in the last decade, including low-dose antipsychotics and psychostimulants, which can induce very rapid remissions often as rapid as several days or weeks. The likelihood of remission will be reduced and the time to remission extended for many melancholic depressive patients if (i) only a narrow-action antidepressant is prescribed, (ii) the patient has a previously undeclared or undetected bipolar disorder (with melancholic depressive episodes), or (iii) is a rapid metabolizer of medication—as generally indicated by the complete absence of side effects and a lack of clinical improvement.

The nonmelancholic depressive conditions are heterogeneous and include depressive disorders induced by stress (eg, reactive depression, situational depression) and/or by personality style. The “reactive” conditions are to some degree simply more severe forms of “normal depression” where the depressive state is either self-limiting or highly responsive to environmental factors and the skills of the therapist. It is well recognized that the “placebo response” rate in controlled antidepressant drug trials is in the order of 40% to 60%—for both those in the active drug and placebo groups. Such subjects include true placebo responders, but also those who experience a “spontaneous remission” and, of relevance here, those where a nondrug intervention (eg, counseling, psychotherapy) will have induced a remission by effectively negating or neutralizing the impact of the depression-inducing stressor, or by effecting recognized nonspecific therapeutic ingredients (eg, empathy, optimism) that can be substantive. Functional remission will be slower (or not achieved) if the depressogenic stressors are unable to be redressed, if the patient has substantive anxiety or a personality disorder, if a therapeutic alliance is difficult to establish, if medication adherence is poor, or again if the wrong treatment is adopted.

**What are the therapeutic goals necessary to achieve optimal global functioning?**

Therapists vary in their emphases on making a diagnosis and formulation versus giving prominence to the patient’s narrative or life story, though they should not be positioned as mutually exclusive. I view the former as a central first step in setting the target of achieving a remission in a depressed patient. A diagnosis allows the clinician to logically select the most appropriate treatment options, while a formulation (explaining why “this” individual has “this” type of depression at “this” particular time) allows the therapist to factor in predisposing and precipitating causes for redressing in the management plan. As observed by Kahneman,³ “To be a good diagnostician, a physician needs to acquire a large set of labels for diseases, each of which binds an idea of the illness and its symptoms, possible antecedents and causes, possible developments and consequences, and possible interventions to cure or mitigate the illness.” A “diagnosis” is also important to the patient, with Montgomery⁴ observing “Just having a diagnosis means that the rest of your life can start... to know the cause of disease is to have control... patients want to know what is wrong, if it is serious, how long it will last, whether it will alter their life plans.”

A valid diagnosis is distinctly more likely to promote remission as it will shape the choice of the most appropriate treatment modality and the way in which it should be applied, whether sequentially (eg, initially prioritizing the patient’s melancholic depression by medication and then addressing his/her alcoholism with a specific program) or pluralistically (eg, if multiple modalities are used such as antidepressant medication and...
psychotherapy, how are they best assembled and combined). Many authors (eg, Petersen) have considered the evidence and articulated a rationale for combination pharmacotherapy and psychotherapy. Thus, the initial priority in managing a depressed individual is to determine whether the condition is unipolar or bipolar, a melancholic or nonmelancholic depression, and the contributing etiological factors that will require specific attention. That priority should be reprioritized if a full remission is not achieved in a reasonable period.

Establishing a therapeutic alliance is a worthy objective but achieving it in managing some depressive conditions (eg, psychotic depression) may be impossible or compromised by the gravity of the patient’s mood state. While involving family members is generally a wise general strategy (albeit respecting confidentiality issues), this may be central when the therapeutic alliance is problematic.

After deriving a diagnosis and formulation I believe that the therapist should be open with the patient and indicate the logical management steps. In managing some clinical scenarios (eg, bipolar depression) a precise and logical initial plan may be difficult to derive. In such circumstances I recommend an optimistic general statement (eg, “I have no doubt that we can get your mood swings under control but I cannot guarantee whether the first, second, or even third medication will do the job, so we will review progress on a regular basis”). Such a communication should have three key components. Firstly, to offer hope at a realistic level so that, if there is no response to the first intervention, the practitioner does not lose his/her credibility. Secondly, to generically explicate a sequential model, with only one treatment component being changed at any one time (to evaluate impact unconfounded by multiple changes). Thirdly, to keep in close contact with the patient—be it weekly, fortnightly or, in rare cases, daily.

If improvement to remission is not proceeding as expected, it is necessary to investigate why. For example, is the initial diagnosis incorrect and, as a consequence, is there a paradigm failure (ie, the treatment—drug or nondrug—is inappropriate for the condition)? Could there be a nondepressive primary diagnosis? (eg, Parkinson’s disease). Is the patient taking his/her medication correctly or “forgetting” (another reason for involving family members)? Is the medication ineffective because the patient’s alcohol consumption is excessive? Do side effects (or their absence) indicate that the patient may be a slow or rapid metabolizer? Have medical factors (eg, hypothyroidism, sleep apnea) been ruled out, and should a brain scan be undertaken to exclude any cerebral factor (especially hyperintensities)? If medication is the dominant modality, are there other factors (eg, severe independent anxiety, major financial problems, personality disorder, and marital difficulties) that would benefit from counseling, psychotherapy, or practical assistance? If the patient is still failing to improve then seeking a second opinion can often be wise.

**What properties are necessary for antidepressants to achieve optimal functional remission?**

Most formal recommendations weight “an” antidepressant being prescribed at a sufficient dose and for a “suitable period,” and often recommend the maintenance therapy principle that “the dose that gets you well should be continued to keep you well.”

While in broad agreement, I have a few qualifications and additional points to offer. I do not regard all antidepressants as equally effective across differing depressive disorders. If using an antidepressant for a nonmelancholic disorder, a narrow-action medication may be sufficient while, as noted earlier, a broader-action medication such as a tricyclic antidepressant—as well as augmentation strategies—may be necessary to bring a melancholic episode to remission.

I tend to commence the antidepressant at half the recommended starting dose in case the patient is a slow metabolizer, and build to the recommended dose in 1 to 2 weeks. While it is commonly stated that all antidepressants can take many weeks or months to work, the evidence challenges that mythology. In essence, if an antidepressant is likely to induce a remission then some evidence of improvement (ie, a reduction of 20% or more in the severity of mood symptoms) should be observed in the first 10 days. Thus, if a patient with melancholia has not responded to an adequate dose after 2 to 3 weeks, I move to augmentation or to a different antidepressant rather than wait for any more extended a period. As noted earlier, factors that may impede or advance remission include identification of the depressive subtype and recognition that differing depressive conditions show quite differential responses to differing medications and nondrug strategies, and concurrent drug and alcohol use, drug metabolizing status and presence of certain organic conditions. Patients who employ a wellbeing plan (ie, incorporating exercise, anxiety reducing strategies, dietary control, and augmentation with fish oil) tend to be more likely to achieve functional remission, as do those who are open rather than feeling stigmatized about their condition. Other authors have overviewed and detailed nuances of such an “integrative approach” to management.

**Which associated strategies are useful to achieve functional remission?**

In most patients with a biological depression (ie, melancholic, psychotic, bipolar), medication alone (whether as monotherapy or in combination or with use of an augmenting strategy) may suffice, even when the patient may have major stressors in their life—whether causes or consequences of the depression. Such depressive conditions are associated with profound anergia and most patients will tend to stay in bed for extended periods while a significant minority with “atypical” hypersomnia will sleep excessively. Encouraging such
patients to get out of bed early and engage in exercise (despite their innate resistance) can be distinctly helpful. For those who are shift workers, stabilizing their work hours can be fundamental. Reducing the stress load associated with work or school can be of some assistance. Advising the patient’s relatives as to how to best offer support will not only be of some benefit to many patients, but may redress the propensity for some relatives to be critical or judgmental of the patient. Regular review by the clinician is important for monitoring progress, while the clinician should be directly and indirectly advancing hope—so that the patient learns over episodes the important mantra that “This too will pass.” Kurian et al have provided a useful and practical overview of medication-based strategies for targeting key residual symptoms.

For those with a nonmelancholic depression, concomitant treatment strategies are often best crafted by examining possible episode determinants. For example, if anxiety has predisposed or precipitated an episode, then anxiety-reducing strategies should be included in the management plan. Predisposing personality nuances may benefit from psychotherapy, while many of the stressors and collateral damage generated by the episode (eg, marital discord) should be addressed, often most readily by counseling. The therapeutic ingredients brought by the clinician to managing nonmelancholic depression may have a substantive impact, so choosing a caring, competent, and readily available managing clinician is fundamental.

It is useful to examine strategies nominated by patients who have done well in managing their depressive episodes, and I abstract the principal ones from accounts of several hundred patients. They included adopting personal philosophical approaches (eg, live one day at a time; accept that the black dog is not your fault; affirm yourself as a worthwhile person; find glimmers of hope and swim toward them; focus on and appreciate the simpler things in life; never be sorry for yourself), socializing (eg, find a support group or rely on a key friend), planning and structuring the days, having a “happy folder” to record positive moments, exercising, and introducing de-stressing strategies (eg, meditation, yoga, avoiding talk back radio, and abandoning deadlines for healing). Such “inside out” perspectives complement and enrich the “outside in” literature on advancing remission.

References

Keywords: antidepressant; depression; functional outcome; remission; treatment

VERS LA RÉMISSION COMPLÈTE : AMÉLIORATION DES RÉSULTATS FONCTIONNELS DANS LA DÉPRESSION

Le terme de rémission diffère quelque peu dans sa signification et sa définition opérationnelle selon qu’il s’agit du patient, du médecin ou du chercheur. L’auteur répond dans une perspective clinique à cinq questions posées par l’enquêteur. Une telle approche donne au diagnostic et à la formulation toute leur importance, surtout en identifiant les sous-types dépressifs particuliers et leurs causes probables, les deux pouvant modéler, sinon dicter, les priorités thérapeutiques et les nuances de la prise en charge. Si la rémission ne survient pas, l’étape logique suivante est de revoir le diagnostic et d’étudier les facteurs pouvant empêcher les progrès.
Background: Impairment in psychosocial functioning, including social and occupational/role functioning, is common in individuals with depression, and improving functional outcomes should be an important goal of depression treatment. There are many standardized assessments of functioning available to help clinicians and researchers better measure and monitor functional outcomes, but these are employed much less frequently and consistently than symptom severity scales in clinical trials and clinical settings.

Method: We review the issues and challenges in defining, measuring, and monitoring functional outcomes in depression, in particular the advantages and disadvantages of self- versus clinician-rated scales and other assessment methods. We also provide examples of validated assessments, with a focus on measures of occupational functioning, a particularly important outcome both for patients and society.

Results: Psychosocial functioning outcomes are distinct from symptomatic and quality of life outcomes. They can be objective (ie, directly quantifiable), or more subjective (ie, based on patient perspectives) and captured through self-report and clinician ratings and observations, methods that offer distinct advantages and disadvantages. Selecting assessments depends on a number of factors, including psychometrics, reason for use, context, patient population, and setting. Conclusions: Improving functional outcomes begins with valid, reliable, and sensitive assessments that are appropriate for the purpose at hand. Fortunately, a wide range of tools are available. Such scales should be used to assess, monitor, and ultimately improve psychosocial outcomes in depression.

Assessments of functional improvement: self- versus clinician-ratings

by V. C. Evans and R. W. Lam, Canada
and to track any changes in functioning that occur over time (eg, with treatment, between episodes of depression, etc). A number of assessment tools have been developed and validated to assess functioning, both generally and in depression specifically. However, there is much variability in assessments, and there are many important considerations in selecting appropriate measures of functioning.

In this paper, we briefly review the issues surrounding defining, measuring, and monitoring functional outcomes in depression. We begin with a discussion of the differences between functional and symptomatic outcomes, quality of life, and “subjective” versus “objective” measures of functioning. Next, we outline some of the challenges in assessing functional outcomes in MDD, and the advantages and disadvantages of self- versus clinician-rated and other assessment methods. Finally, we describe some of the commonly used assessments of functioning in depression. Because of increasing clinical, research, and policy attention on depression in the workplace, we also highlight some assessments of occupational functioning.

What are functional outcomes and how are they different from symptom outcomes and quality of life?

Psychosocial functioning has been broadly defined as “one’s ability to perform the tasks of daily life and to engage in relationships with others in ways that are gratifying to the individual and others that meet the needs of the community.”

Within this definition, there are many ways to construe which domains of functioning constitute the “tasks of daily life” in a given society and culture. However, certain broad domains have been recurrently identified and evaluated in assessments of functioning; these include occupational or role (eg, student or other roles); household; social, including within the family (marital, parental, immediate, and extended), with friends, or in the community; leisure and recreational; self-care; and physical functioning.

The core symptoms of depression, including affective (sad/low mood, anhedonia, guilt, low self-esteem), cognitive (eg, lack of motivation, difficulty with concentration, thinking, and memory, cognitive slowing), and somatic (changes in sleep, appetite) clusters, contribute substantially to psychosocial impairment in depression. However, although they are clearly related, functional status is not fully explained by the severity of depressive symptoms. For example, there is a variable range of correlations between scores on symptom and functioning scales in depression. Improvement in psychosocial functioning may lag behind symptomatic improvement and functional impairment may persist between episodes of depression, even during symptom remission. Although the causes of such persistent functional impairments are likely multifactorial and heterogeneous, contributing factors may include residual depressive and cognitive symptoms, medication side effects, psychiatric and medical comorbidities, and behavioral consequences of depression (eg, social isolation). Because functional improvement is not tightly correlated with symptomatic improvement, monitoring of outcomes in the treatment of depression should include assessment of both symptoms and functioning.

Another distinction is that between functioning and quality of life (QOL). Both are important and related concepts that are occasionally conflated or included under the umbrella of “psychosocial functioning.” The World Health Organization has described QOL as an “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.” That is, QOL is an inherently subjective measure based on self-perception and context with an emphasis on satisfaction, contentment, or enjoyment in various aspects of life. In contrast, functioning is more so understood to reflect one’s actual behavior in the world and assessed in ways that emphasize doing, performing, maintaining, etc.

An example of a QOL scale is the Medical Outcomes Study Health Survey–Short Form (SF-36). The SF-36 is a 36-item self-report scale that assesses health-related QOL and subjective health outcomes across different physical and mental health conditions. Although it is commonly referred to as a scale to assess functioning, the SF-36 only includes a few items on the impact of physical and mental health issues on activities of daily life that would be considered indicators of functioning. For the purposes of this paper, we will focus on functional measures and exclude discussion of QOL measures.

Assessment of functioning, however, can also be “subjective” (ie, relying on patients’ perceptions of their level of functioning) or “objective” (ie, directly quantifiable, eg, employment status, number of hours worked, frequency of attending social events, etc.). Subjective functional outcomes may be especially important in determining patient satisfaction and perspective for evaluating the success of treatment.
How do we assess functional outcomes in depression? Considerations, challenges, and differences among assessments of functioning

In addition to subjective versus objective measures, there are other considerations and challenges in assessing functional outcomes in depression that will inform the selection of assessments. One major consideration is the modality of evaluation—self-rated by the patient, clinician-rated based on patient report (usually with clinical or structured interviews), or observer-rated through direct observations or laboratory tasks. Table I summarizes the advantages and disadvantages of these modalities.

Self- and clinician-rated assessments can both be used to gather objective and subjective information about functioning. For example, the self-rated Social Functioning Scale (SFS), originally developed to assess social functioning in individuals with schizophrenia, includes items that would be considered both subjective (eg, “How easy do you find talking to people at the moment?”) and more “objective” (eg, frequency of participating in various social activities over the past three months, such as visiting relatives, visiting friends, playing an outdoor sport, etc). A major issue with self-rated instruments is the potential for respondent bias, especially given that depression is associated with negative self-perceptions. Clinician-rated assessments may have an advantage if clinical expertise is utilized to gain a more accurate evaluation of a patient’s actual level of functioning. However, clinician expertise and skill in interviewing varies, and even if structured or semi-structured interview guides are used, bias is still possible since they rely on a patient’s self-report during the interview. The drawback of clinician-rated assessments is the time and training required to complete them.

Direct task observation and laboratory tasks can minimize subjective bias, but these can be time-consuming and complicated and may be affected by other forms of depressive bias (eg, lack of motivation to participate in a task). One example of an observation-based task that has been used in schizophrenia and depression research is the Social Skills Performance Assessment (SSPA). Patients are scored on their performance in two brief, standardized role-play tasks: introducing oneself to a stranger and addressing an issue with a landlord.

◆ Selection of functioning assessments

Selection of assessments will depend on a number of factors, including psychometrics, reason for use, context, patient population, and setting. All assessments need to demonstrate adequate psychometric properties, including consistency, validity, and reliability.

Some assessments are global, consisting of as few as one or two items that capture a patient’s overall level of functioning in, for example, work, household, and social domains, as in the Sheehan Disability Scale (SDS). Others assess multiple dimensions and may include several dozen items to collect more detailed information. The latter inevitably take longer and carry a greater burden for patients and clinicians to complete, but are necessary when the goal of the assessment is a more comprehensive understanding of functioning.

The purpose and context of the assessment will thus obviously affect the type of scale to be used. In research settings, more detailed and longer assessments are often necessary. For example, some scales are designed to capture theoretical constructs in psychosocial functioning, which generally
include several dimensions, each requiring a number of items. In clinical trial settings, it is especially important that scales demonstrate sensitivity to change and ability to detect clinically important differences between treatments. In busy clinical settings, functional assessments must collect clinically relevant information to inform diagnosis and treatment decisions, and to monitor changes in functioning over time. Such scales need to be brief, acceptable to patients and clinicians, and easy to administer.

Assessments must also be appropriate for the target population, so demographics and social and cultural context should be taken into account. Finally, scales vary by the time frame of assessment, ranging from the past week, the past month, to the past several months, which may also impact their utility. For a 6-week randomized controlled trial of an acute intervention for depression, a scale designed to assess functioning in the past month may be less sensitive to change than one assessing the past week.

In the following sections, we highlight some of the commonly used measures of functioning in depression, including global and multidimensional assessments and more specific assessments of social and occupational functioning.

Global and multidimensional assessments of psychosocial functioning

Many existing assessments of functioning are designed to evaluate more than one major domain of functioning, such as work/occupational, social, and household functioning, usually with one or two global items. There is a good range of self- and clinician-rated options available, examples of which are listed and described in Table II (page 516-517). The advantage of such scales is to provide information on several important functional domains that may be differentially impaired, all within a single, brief scale.

◆ Clinician-rated scales

With regard to clinician-rated global scales, the single-item Global Assessment of Functioning scale (GAF), which served as a measure of overall psychiatric disturbance and functioning (Axis V) of the DSM-III-R and DSM-IV, has been widely used in clinical settings. The GAF is flawed, however, as an assessment of functioning because it conflates symptoms with functioning. To address this limitation, the Social and Occupational Functioning Assessment Scale (SOFAS) was devised. The SOFAS is identical to the GAF except that the symptom components of the anchor points are removed, so that only functional impairment is assessed. The SOFAS is a single global score from 1 to 100, with lower scores indicating greater difficulties in functioning.

Other multidimensional assessments of functioning are more detailed than these global scales. For example, the clinician-rated Multidimensional Scale of Independent Functioning (MSIF) assesses three different functional domains (work, household, and education, if applicable) by considering separately the degree of role responsibility, role support, and performance in each. These can be important factors in assessing functioning which are obscured in other global assessments.

The Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool (LIFE-RIFT) is another multidimensional clinician-rated scale that is a good example of an assessment that incorporates items for both functioning and QOL. Validated for use in populations with MDD, the LIFE-RIFT scale assesses functioning in the domains of work (most impaired of: occupational, household, and educational functioning), interpersonal relations (most impaired relationship of: relationship with spouse, children, other relatives, or friends), recreation, and satisfaction, which is an item on global QOL.

Finally, in the new DSM-5, the World Health Organization’s Disability Assessment Schedule (WHODAS) has been recommended to replace the GAF as a routine assessment of functioning and disability. The WHODAS is available as 36- and 12-item versions with items on cognitive functioning, mobility, self-care, social, life activities (household and occupational/educational functioning), and participation in the community. It is used across health conditions and mental disorders and can produce standardized disability scores, with general and clinical population norms also available. It is available in clinician-rated, self-rated, and proxy-rated formats.

◆ Self-rated scales

There are a number of brief self-rated, global assessments of functioning as well. The Sheehan Disability Scale, described previously, and the Work and Social Adjustment Scale (WSAS), consisting of one item each on occupational, household, and social functioning, private leisure, and close relationships, are good examples of such scales.

One of the most widely-used assessments of psychosocial functioning in research studies is the Social Adjustment Scale (SAS), a 54-item self-report scale that looks at performance, interpersonal friction, and feelings and satisfaction in work (occupational, household, educational), and social (social, leisure activities, relationships with extended family, role as a marital partner, role as a parent, and role within the family unit) domains.

Another interesting multidimensional scale is available from the Patient Reported Outcome Measurement Information System (PROMIS). PROMIS is an initiative of several research centers that is funded by the US National Institutes of Health to provide highly reliable and valid assessments of patient-reported health, including physical, mental, and social well-being. Scales are standardized and comparisons are available across many different chronic health conditions, including de-
pression. PROMIS has developed one self-report assessment of functioning, the “Ability to Participate in Social Roles and Activities” Short Form, which consists of 8 items assessing functioning in work (including occupational and household), social activities with family and friends, and leisure.

Assessments of occupational functioning
Most people with MDD experience impairments in their occupational functioning: they miss more days of work than those who are not depressed,
and report being less productive when at work.
Occupational functioning is obviously important to patients, who might fear or experience a loss of livelihood and attendant financial and social stress, and to employers, organizations, and society, which incur the costs of unemployment, long-term disability, absenteeism, and presenteeism.

Like other domains of functioning, assessment of work functioning and productivity can include objective (eg, hours of work missed) and subjective measures (eg, self-reported mistakes at work). Employment status, disability status, and time absent from work due to illness may appear to be more “objective” measures of work functioning than self-report measures of productivity. However, the former can be influenced by many external and corporate factors unrelated to illness, such as the availability of sick days, disability leave and insurance, flexibility in work hours, and accommodations at work, among others. While absenteeism can be used as an outcome measure in studies and clinical trials, there is often a skewed sample distribution.

There are also challenges in measuring productivity and presenteeism. It is difficult to objectively assess productivity based on units of output because these will vary widely across different occupations and will not be possible to quantify for many. For example, how is productivity measured objectively in physicians or nurses? Even when productivity output is quantifiable, important factors such as the amount of time or effort expended to produce that output may not be assessed.

Self-reports about performance at work are much more easily obtained and may be the only method to collect productivity information.

Table II. Examples of global and multidimensional assessments of psychosocial functioning.

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<thead>
<tr>
<th>Assessment</th>
<th>Administration modality</th>
<th>Dimensions of functioning assessed</th>
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<tbody>
<tr>
<td>Longitudinal Interval Follow-up Evaluation- Range of Impaired Functioning Tool (LIFE-RIFT)</td>
<td>Clinician-rated; requires a semi-structured interview</td>
<td>Work (most impaired of occupational, household, and educational), social, life satisfaction (quality of life), and recreation</td>
</tr>
<tr>
<td>Multidimensional Scale of Independent Functioning (MSIF)</td>
<td>Clinician-rated; requires a semi-structured interview</td>
<td>Occupational, educational, and household</td>
</tr>
<tr>
<td>Role Activity Performance Scale (RAPS)</td>
<td>Clinician-rated; requires semi-structured interview (including opportunities to collect collateral information)</td>
<td>Occupational, educational, household, social, leisure, self-care</td>
</tr>
<tr>
<td>Role Functioning Scale (RFS)</td>
<td>Clinician-rated</td>
<td>Work (occupational, educational, or household), self-care, social</td>
</tr>
<tr>
<td>Social and Occupational Functioning Assessment Scale (SOFAS)</td>
<td>Clinician-rated</td>
<td>Occupational (including educational), social</td>
</tr>
<tr>
<td>World Health Organization’s Disability Assessment Schedule (WHODAS 2.0), 36- and 12-item versions</td>
<td>Clinician-rated; interview, self-administered, and proxy versions available</td>
<td>Work (occupational, household, and educational), psychosocial (getting along with others, participation in community); some items assess QOL</td>
</tr>
<tr>
<td>Sheehan Disability Scale (SDS)</td>
<td>Self-report</td>
<td>Occupational, social, household</td>
</tr>
<tr>
<td>Work and Social Adjustment Scale (WSAS)</td>
<td>Self-report</td>
<td>Occupational, household, social leisure, private leisure, close relationships</td>
</tr>
<tr>
<td>Patient Reported Outcome Measurement Information System (PROMIS) “Ability to Participate in Social Roles and Activities” Short Form</td>
<td>Self-report</td>
<td>Social (including activities with family and friends), work (including occupational and household), leisure</td>
</tr>
<tr>
<td>Social Adaptation Self-evaluation Scale (SASS)</td>
<td>Self-report</td>
<td>Social</td>
</tr>
<tr>
<td>Social Adjustment Scale II (SAS)</td>
<td>Self-report, proxy report versions</td>
<td>Work (occupational, household, educational), Social (social, leisure activities, relationships with extended family, role as a marital partner, parent, and within family unit; some items assess QOL</td>
</tr>
<tr>
<td>Social Functioning Scale (SFS)</td>
<td>Self-report</td>
<td>Social, recreation, self-care, and occupational</td>
</tr>
<tr>
<td>Social Skills Performance Assessment (SSPA)</td>
<td>Performance-based (laboratory task)</td>
<td>Social competence</td>
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### Assessments of functional improvement: self- versus clinician-ratings – Evans and Lam

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<table>
<thead>
<tr>
<th>Brief description</th>
<th>Validation/Use</th>
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<tbody>
<tr>
<td><strong>9 items</strong></td>
<td>Assesses global impairment over the past week, in work (most impaired of employment, household, and education items), social (most impaired relationship with family (spouse, children, other relatives) and friends), life satisfaction, and recreation, each on a 5-point scale (1 = no impairment, 5 = severe impairment); subscale scores can then be summed to yield a global score.</td>
</tr>
<tr>
<td><strong>9 items</strong></td>
<td>Assesses degree of (a) role responsibility, (b) role support, and (c) performance over the past month, in work, education, and household items, each on a 7-point scale (1 = normal functioning, 7 = total disability).</td>
</tr>
<tr>
<td><strong>12 domains, 8-16 interview questions each</strong></td>
<td>Assesses role functioning over up to the past 18 months in the following 12 domains (if applicable): work/work equivalent, education, household, family relationships, mate relationships, parenting, social relationships, leisure activities, self-management, health care, hygiene/appearance, and rehabilitation treatment settings. Clinician scores functioning in each domain on a 6-point scale, from 1 (excellent or good) to 6 (severely or completely impaired).</td>
</tr>
<tr>
<td><strong>4 items</strong></td>
<td>Assesses global functioning over the past month, in 4 domains: primary work role (occupational, educational, household), independent living/self-care, and immediate and extended social relationships, each on a 7-point scale (1 = severe impairment, 7 = optimal functioning).</td>
</tr>
<tr>
<td><strong>1 item</strong></td>
<td>Assesses current social and occupational functioning with a single global score from 0–100, higher scores indicating better functioning. Identical to Global Assessment of Functioning scale (GAF) but excludes symptom severity from anchor points.</td>
</tr>
<tr>
<td><strong>36- &amp; 12-item versions</strong></td>
<td>Assess difficulties in the following domains over the past 30 days: cognitive functioning, mobility, self-care, getting along with others, life activities (work, including occupational, household, and educational work), and participation in community (including items on QOL: stigma, leisure, etc.), each rated on a 5-point scale from 0 (none) to 5 (extreme).</td>
</tr>
<tr>
<td><strong>5 items</strong></td>
<td>Assesses perceived disruption to occupational, social, and household functioning over the past week, with one item each, rated on a 10-point visual analog scale (0 = not at all, 10 = extremely), plus days lost and days unproductive.</td>
</tr>
<tr>
<td><strong>5 items</strong></td>
<td>Assesses global impairment in 5 domains on a 9-point scale, from 0 (not at all) to 8 (very severely): occupational, household, social leisure, private leisure, and close relationships.</td>
</tr>
<tr>
<td><strong>4-, 6-, and 8-item versions</strong></td>
<td>Assesses perceived ability to perform usual social roles and activities (e.g., “I have to limit my regular family activities”, “I have trouble doing all of my usual work (including work at home)” on a 5-point scale (1 = always, 5 = never). See <a href="http://www.nihpromis.org">www.nihpromis.org</a> for more information on PROMIS scales.</td>
</tr>
<tr>
<td><strong>21 items</strong></td>
<td>Assesses aspects of social interactions, global social attitude, and self-perception.</td>
</tr>
<tr>
<td><strong>54 items</strong></td>
<td>Items in each domain assess performance, interpersonal friction, fine-grained aspects of interpersonal relations, and feelings/satisfaction, rated on a 5-point scale, higher scores indicating greater impairment. Generates 6 domain scores.</td>
</tr>
<tr>
<td><strong>~35 items</strong></td>
<td>Assesses social withdrawal, interpersonal functioning, social activities, recreational activities, independence (self-care), and occupational functioning.</td>
</tr>
<tr>
<td><strong>2 tasks</strong></td>
<td>Assesses social competence through role-playing in two different, brief social situations.</td>
</tr>
</tbody>
</table>
jective measures of productivity have their own unique measurement issues.\textsuperscript{44} For example, there are different methods to query productivity; by having respondents rate impairment directly, compare current performance to “usual” performance or the performance of an average worker in that role, estimate percentage of unproductive time at work, etc, all of which may assess slightly different constructs of presenteeism.

Also, few productivity and work functioning scales have been validated against objective measures (for a thorough discussion of these issues, see Brooks et al, 2010\textsuperscript{44}).

\textbf{Work functioning scales}

Notwithstanding these important issues, many existing assessments of occupational functioning, including absenteeism and presenteeism, are self-report scales. The majority are developed for use across various health conditions.

Table III lists examples of some of the common scales for occupational functioning. The World Health Organization’s Health and Work Performance Questionnaire (HPQ)\textsuperscript{46} is perhaps the “gold standard” assessment of occupational functioning. The HPQ is one of the few self-rated scales that has been validated against objective measures of productivity\textsuperscript{52} and used in large randomized controlled trials in MDD.\textsuperscript{53} However, at 44 items and 8-12 pages, it is too long to be practical for use in clinical settings.

The Work Limitations Questionnaire (WLQ)\textsuperscript{50} is another well-researched and widely used assessment of presenteeism in chronic health conditions. The WLQ is available in a 25-item (full-length) version and a shortened 8-item version. Because it was developed to measure productivity across a range of general health conditions, it queries the impact of both physical health and emotional problems on functioning.

To fully capture the nature and extent of work impairment due to mental disorders such as depression, it may be necessary to use assessments of functioning specifically designed for that population. A recent review and comparison of productivity scales for use in mood disorders\textsuperscript{54} identified only two scales specifically validated in MDD: the Endicott Work Productivity Scale (EWPS)\textsuperscript{45} and the Lam Employment Absence and Productivity Scale (LEAPS).\textsuperscript{48} The LEAPS was developed

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Administration modality</th>
<th>Brief description</th>
<th>Validation/Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endicott Work Productivity Scale (EWPS)\textsuperscript{45}</td>
<td>Self-report</td>
<td>(28 items). Assesses work productivity, with 25 items on presenteeism and additional items on absenteeism (expected hours, hours actually worked, and reason for working less, if applicable), over the past week. Presenteeism items are rated on a 5-point scale of frequency, (0 = never, 4 = almost always)</td>
<td>Developed specifically for use in psychiatric and depressed samples. Validated in samples of both depressed outpatients and of the community</td>
</tr>
<tr>
<td>Health and Work Performance Questionnaire (HPQ)\textsuperscript{46,47}</td>
<td>Self-report</td>
<td>(22 items). Assesses absenteeism, special work achievements, failures/accidents, and presenteeism, with items on performance relative to other workers and on specific productivity-related behaviours rated on 5- and 10-point scales, over a combination of the past week and past month</td>
<td>Developed for use across a number of health conditions</td>
</tr>
<tr>
<td>Lam Employment Absence and Disability Scale (LEAPS)\textsuperscript{48}</td>
<td>Self-report</td>
<td>(10 items). Consists of one item on occupation, two items to assess absenteeism, and seven items to assess presenteeism, according to both symptoms most reported to interfere with work functioning in depression (eg, Poor concentration or memory) and behaviors associated with productivity (eg, Getting less work done), over the past 2 weeks. Presenteeism items are rated on a 5-point scale of frequency (0 = none of the time, 0%, 5 = all of the time, 100%)</td>
<td>Developed specifically for use in clinically depressed, currently employed samples. Validated in a sample of depressed outpatients</td>
</tr>
<tr>
<td>Stanford Presenteeism Scale (SPS)\textsuperscript{49}</td>
<td>Self-report</td>
<td>(6 items). Assesses presenteeism over the past month with items on stress, focus, and energy at work, rated on a 5-point scale (1 = strongly disagree, 5 = strongly agree), with higher scores indicating better functioning. Yields single score with 2 factors: completing work and avoiding distractions</td>
<td>Developed for use across a number of health conditions</td>
</tr>
<tr>
<td>Work Limitations Questionnaire (WLQ)\textsuperscript{50}</td>
<td>Self-report (25- and 8-item versions)</td>
<td>Assesses presenteeism, with items on time management, and managing physical, mental/interpersonal, and output demands, rated on a 5-point scale (0 = all of the time, 4 = none of the time), over the past 2 weeks</td>
<td>Developed for use across a number of health conditions, eg, angina, osteoarthritis, etc</td>
</tr>
<tr>
<td>Work Productivity and Activity Impairment (WPAI)\textsuperscript{51}</td>
<td>Self-report</td>
<td>(6 items). Assesses absenteeism (hours missed from work), one item on presenteeism (how much the health issue affected ability to do work), and one item on daily life activities</td>
<td>Developed for use across a number of health conditions</td>
</tr>
</tbody>
</table>

\textit{Table III.} Examples of assessments of occupational functioning.
to be a clinically useful measure of work impairment, assessing symptoms found to be most associated with occupational impairment in depression (eg, low energy or motivation, poor concentration or memory) as well as reduced work performance (eg, getting less work done, making more mistakes). It is sufficiently brief to be used in clinical settings but sensitive to changes with depression treatment.

Conclusions
Functioning is important to individuals and to society. Impairment in functioning is a defining feature of MDD and psychiatric illnesses in general. Hence, functional outcomes must be assessed along with symptomatic and quality of life outcomes in research and treatment for depression. Improving functional outcomes begins with valid, reliable, and sensitive assessments of functioning that are appropriate for the purpose at hand. Fortunately, there is a wide range of tools available, from global and multidimensional assessments to detailed scales of specific domains such as social and occupational functioning.

When selecting a scale, clinicians and researchers must consider the type of information to be collected and the purpose of the assessment. Clinician-rated measures may provide additional information if the assessment is informed by clinical expertise, and laboratory paradigms can be useful in research settings. Assessments must demonstrate sensitivity to change if used for clinical trials. Brief, simple, patient-rated scales are usually most feasible for busy clinical settings. Used appropriately, assessments of functioning will serve as important tools for assessing, monitoring, and ultimately improving functional outcomes in depression.

References
ÉVALUATION DE L’AMÉLIORATION FONCTIONNELLE :
AUTO-ÉVALUATION VERSUS ÉVALUATION PAR LE MÉDECIN

Historique : La détérioration du comportement psychosocial, y compris du comportement social et professionnel, est courante chez les personnes déprimées, l’amélioration des résultats fonctionnels doit donc être un objectif important du traitement de la dépression. De nombreuses évaluations standardisées du comportement sont disponibles pour aider les médecins et les chercheurs à mieux mesurer et contrôler les résultats fonctionnels, mais elles sont beaucoup moins fréquemment et beaucoup moins régulièrement employées dans les études et les tableaux cliniques que les échelles de sévérité des symptômes. Méthodes : Nous analysons les problèmes et les enjeux de la définition, de la mesure et de la surveillance des résultats fonctionnels dans la dépression, en particulier les avantages et les inconvénients des échelles d’auto-évaluation versus les échelles d’évaluation par le médecin et d’autres méthodes d’évaluation. Nous donnons aussi des exemples d’évaluations validées, en insistant sur les mesures du comportement professionnel, particulièrement importantes pour les patients et la société. Résultats : Les résultats du comportement psychosocial sont distincts des résultats symptomatiques et de qualité de vie. Ils peuvent être objectifs (c’est-à-dire directement quantifiables) ou plus subjectifs (c’est-à-dire basés sur le point de vue des patients) et recueillis à partir d’observations et d’auto-évaluations ou d’évaluations faites par un médecin, méthodes qui présentent des avantages et des inconvénients différents. Les modalités d’évaluation dépendent d’un certain nombre de facteurs, comme la psychométrie, la raison d’utilisation, le contexte, la population des patients et les circonstances. Conclusions : L’amélioration des résultats fonctionnels commence par des évaluations solides, fiables et sensibles, adaptées aux besoins de la cause. Heureusement, nous disposons d’une large gamme d’outils. De telles échelles devraient être utilisées pour évaluer, surveiller et enfin améliorer le volet psychosocial de la dépression.

Keywords: assessment; major depression; occupational functioning outcome; psychosocial functioning outcome
An effort was made to refine the distinction between normal bereavement and the symptoms associated with a major depressive episode. Certainly, bereavement can be associated with a high degree of suffering, but it generally does not result in a major depressive episode. By eliminating the “bereavement exclusion,” the DSM-5 clarifies that bereavement is typically longer than 2 months (an incorrect implication of the bereavement exclusion).”

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Last year (May 2013), a major update in the area of psychiatric nomenclature was published, namely the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). This revision occurred after a multi-year interdisciplinary effort by several hundred scientists and clinicians who updated diagnostic criteria and clinical descriptions for all psychiatric disorders. First, consideration of development across the lifespan led to changes in the overall chapter structure and the order of how individual disorders were listed and described within each chapter. Second, more direct attention was given to assessing gender-specific factors within and across disorders. Third, while cultural concerns had previously been raised in earlier versions of the DSM, in DSM-5 specific sections on this topic and a cross-cultural assessment procedure were provided. Fourth, the multiaxial system of psychiatric classification was discontinued and all psychiatric and medical disorders were considered on a single axis. In mood disorders, the most obvious change was the separation of bipolar and related disorders from depressive disorders as individual chapters. There are now 8 specific disorders described in the depressive disorders chapter, including disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Increasing focus has been placed on levels of severity, possible subtypes, and the application of numerous specifiers where appropriate. It is expected that changes in the DSM-5 will enable us to make appropriate changes in diagnostic criteria and specifiers that capture significant advances in clinical research, including advances in neuroscience and genetics.

by D. J. Kupfer, USA

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www.medicographia.com

Last year (May 2013), a major update in the area of psychiatric nomenclature was published, namely the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition). This revision occurred after a multi-year effort by several hundred scientists and clinicians who updated diagnostic criteria and clinical descriptions for all psychiatric disorders. Several key points about this update are worthy of comment. First, this intensive activity, sponsored primarily by the American Psychiatric Association (APA), was conducted in parallel to a similar effort to update the International Classification of Diseases (ICD). Thus, the goal of eventually developing a single classification for mental disorders to be used throughout
the world was facilitated by comparable timelines.\textsuperscript{3} Second, recent advances in clinical and neuroscience research have stimulated numerous discussions—even debates—on how to best integrate such findings into standardized diagnostic criteria.\textsuperscript{4,6} As a result of 13 international conferences and meetings conducted between 2003 and 2008, a greater focus on four important issues was achieved. First, consideration of development across the lifespan led to changes in the overall chapter structure and the order of how individual disorders were listed and described within each chapter. Second, more direct attention was given to assessing gender-specific factors within and across disorders. Third, while cultural concerns had previously been raised in earlier versions of the DSM, in DSM-5 specific sections on this topic and a cross-cultural assessment procedure were provided. Fourth, the multiaxial system of psychiatric classification was discontinued and all psychiatric and medical disorders were considered on a single axis.

### Depressive disorders

- Disruptive mood dysregulation disorder
- Major depressive disorder
- Persistent depressive disorder (dysthymia)
- Premenstrual dysphoric disorder
- Substance/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder
- Unspecified depressive disorder

Table I. Depressive disorders listed in DSM-5.


In the final stages of the review process, the enthusiasm for the inclusion of multiple genetic and neuroscience biomarkers as diagnostic criteria was tempered by the realization that, in most cases, the data were not as definitive as many had hoped.\textsuperscript{7} However, it is likely that the next edition, even a DSM-5.1, should be forthcoming in much less than the 20-year span between DSM-IV and DSM-5. By that time, it would be expected that more diagnostic biomarkers could be included. On this path toward increased use of biological markers for specificity of diagnosis, a larger number of subtypes and specifiers where appropriate.

### Depressive disorders

Given our primary interest in depressive disorders for this report, it is appropriate to point out first the major changes in the depressive disorders chapter. As indicated in Table I, there are now 8 specific disorders described in this chapter, including disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Consistent with previous DSM versions, attention is given to issues of duration, timing, and presumed underlying causes. As discussed later in this review on changes to the depressive disorders, increasing focus has been placed on levels of severity, possible subtypes, and the application of numerous specifiers where appropriate.

A new diagnosis has been added to reflect increasing concern about inappropriate and excessive use of bipolar diagnoses in children. This diagnosis, disruptive mood dysregulation disorder (DMDD), should be used to diagnose children under the age of 12 with persistent irritability and severe behavioral dyscontrol.\textsuperscript{8} The diagnosis is placed in the depressive disorders chapter since the long-term outcome in these children is most likely to be recurrent depression and anxiety disorders, rather than bipolar disorders.\textsuperscript{9}

Major depressive disorder, including major depressive episode, underwent very few changes from DSM-IV to DSM-5. Major depressive disorder is characterized by discrete episodes of at least 2 weeks’ duration (although most episodes last considerably longer) with at least one of two symptoms, either depressed mood or loss of interest or pleasure, and involving changes in affect, cognition, and neurovegetative functioning. While the diagnosis can be based on a single episode, in general the disorder is a recurrent one associated with interepisode remissions in the majority of cases.

Although the classic features of depression have been preserved, an effort was made to refine the distinction between normal bereavement and the symptoms associated with a major depressive episode. Certainly, bereavement can be associated with a high degree of suffering, but it generally does not result in a major depressive episode. By eliminating the “bereavement exclusion,” the DSM-5 clarifies that bereavement is typically longer than 2 months (an incorrect implication of the bereavement exclusion). The added footnotes in DSM-5 further specify the symptom picture associated with bereavement-related major depressive episode, in contrast to uncomplicated bereavement.

In previous DSM editions, a distinction was made between dysthymia and chronic major depressive disorder.\textsuperscript{10} In DSM-5, the diagnosis of persistent depressive disorder captures both the chronic form of major depression and what was formerly dysthymia, a condition that is present for at least 2 years in adults or 1 year in children. Major depression may precede persistent depressive disorder, and major depressive episodes...
Bipolar disorders

- Bipolar I disorder
- Bipolar II disorder
- Cyclothymic disorder
- Substance/medication-induced bipolar and related disorder
- Bipolar and related disorder due to another medical condition
- Other specified bipolar and related disorder
- Unspecified bipolar and related disorder

Table II. Bipolar disorders listed in DSM-5.

mood disorders specifiers

- Anxious distress
- Mixed features
- Rapid cycling
- Melancholic features
- Atypical features
- Psychotic features (mood-congruent / mood-incongruent)
- Catatonia
- Peripartum onset
- Seasonal pattern

Table III. Specifiers listed in the mood disorders chapters of DSM-5.

may occur during persistent depressive disorder. Individuals whose symptoms meet major depressive disorder criteria for 2 years should be given a diagnosis of persistent depressive disorder as well as major depressive disorder.

Premenstrual dysphoric disorder has been moved from an appendix of DSM IV (“Criteria Sets and Axes Provided for Further Study”) to the depressive disorders chapter in DSM-5. This particular disorder has continued to receive much clinical and research attention, as a specific depressive disorder affecting women.11

Finally, as has been noted previously, substances of abuse, certain prescribed medications, and several medical conditions can be associated with depression-like phenomena. The diagnoses of substance/medication-induced depressive disorder and depressive disorder due to another medical condition recognize these issues.12 In addition, the “Not Otherwise Specified” (NOS) category used in DSM-IV has been separated into “other specified” and “unspecified” depressive disorders.

Bipolar disorders

The chapter on bipolar and related disorders is placed between the chapter on schizophrenia spectrum and other psychotic disorders and the chapter on depressive disorders. The chapter placement reflects both the extensive clinical data and emerging neuroscience/genetic data providing a bridge across these nosological areas. The diagnoses included in this particular chapter are bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder (Table II).

Bipolar I disorder does not require the presence of psychosis or the presence/history of a major depressive episode. Nevertheless, most individuals who meet the syndromal definition of mania also experience at least one episode of major depression. The major change to the DSM-5 criteria set for mania is the addition of “increased activity or energy” to criterion A as representing a core symptom of mania and hypomania. The rationale for this change is to increase the clarity and specificity, as well as improving—in particular—the retrospective diagnosis of mania and hypomania.

In contrast, bipolar II disorder includes criteria for both a minimum of one episode of major depression and one episode of hypomania. As noted above, increased activity and energy has been added to the main criterion of hypomania. Secondly, bipolar II disorder is no longer viewed as a “mild” form of bipolar disorder, but one that is also associated with seriously impaired work and family functioning during recurrent episodes. As noted below, the diagnosis of bipolar I disorder, mixed episode in DSM-IV, which required the simultaneous presence of syndromal mania and major depression has been replaced with a new specifier, “with mixed features,” that can be applied to either mania or depression but does not require the simultaneous presence of a full episode of both mania and depression.

The diagnosis of cyclothymic disorder was not changed from DSM-IV and can be made with adults who are experiencing at least 2 years (for children, a full year) of both hypomanic and depressive periods without ever attaining the full syndromal criteria for an episode of mania, hypomania, or major depression.

As is the case with depressive symptoms, many substances of abuse, certain prescribed medications, and several medical conditions can be associated with manic-like phenomena. These features are recognized in the diagnoses of substance/medication-induced bipolar and related disorder and bipolar and related disorder due to another medical condition. Finally, individuals, particularly children and, to a lesser extent, adolescents, who experience bipolar-like phenomena that do not meet the criteria for bipolar I, bipolar II, or cyclothymic disorder can be given the diagnosis of “other speci-
fied bipolar and related disorder.” In addition, specific criteria for a disorder involving short-duration hypomania are provided in Section III of DSM-5 in the expectation of encouraging further study of this presentation, which is particularly common in children who present with bipolar-like symptoms.

In order to provide a more precise assessment, the DSM-5 work groups sought to identify appropriate specifiers in the mood disorders chapters (Table III, page 523). While there had been traditionally a number of specifiers for mood disorders, DSM-5 also includes a number of new specifiers. One such change is the mixed features specifier referred to above. It was intended to address difficulties both in the diagnosis of bipolar disorders and depressive disorders. On numerous occasions, patients experience symptoms consistent with both mania and depression, but not enough for them to reach syndromal status. Therefore, a “with depressive features” specifier was included to be applied to manic or hypomanic episodes when three or more depressive symptoms (depressed mood; diminished interest; psychomotor retardation; fatigue; worthlessness; thoughts of death) are present for the majority of days. In a similar way, the following symptoms may be present during a major depressive episode: elevated mood; increased energy or activity; involvement in pleasurable activities; decreased need for sleep. If they are present for the majority of days, then the “with manic/hypomanic features” specifier can be applied. It is felt that this more inclusive approach to mixed features improves the clinician’s ability to note this important phenomenon.

The second specifier to be added to the mood disorders chapters is one that notes “with anxious distress.” It applies to disorders both in the bipolar and depressive chapters. The anxious distress must be present for the majority of days during the episode and includes at least two symptoms (eg, feeling keyed up; restless; difficulty concentrating; fear that something awful might happen; fear of losing control). Furthermore, with this anxious distress specifier, one can indicate severity by using the number of symptoms present (mild=2; moderate=3; moderate to severe=4-5; and severe=4-5 with motor agitation).

Two additional specifiers not restricted to the mood disorders chapters can be included for use in mood disorder diagnoses. First, a panic attack specifier can be given in the presence of panic attacks during a major depressive episode or even a manic episode. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) symptoms as indicated in Table IV occur. This surge can occur from a calm or anxious state. Secondly, catatonia has now become a specifier that can be used across different diagnostic disorders. The catatonia specifier is appropriate when the clinical picture is characterized by marked psychomotor disturbance and includes intense discomfort that reaches a peak within minutes, and during which time 4 (or more) symptoms as indicated in Table IV occur. This specifier is used to indicate psychosis in the absence of high severity.

### PANIC ATTACK SPECIFIERS (4 or more symptoms):
1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations or shortness of breath or smothering
5. Feelings of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light-headed, or faint
9. Chills or heat sensations
10. Paresthesias (numbness or tingling sensations)
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
12. Fear of losing control or “going crazy”
13. Fear of dying

### CATATONIA (3 or more symptoms):
1. Stupor (ie, no psychomotor activity; not actively relating to environment)
2. Catalepsy (ie, passive induction of a posture held against gravity)
3. Waxy flexibility (ie, slight, even resistance to positioning by examiner)
4. Mutism (ie, no, or very little, verbal response [Note: not applicable if there is an established aphasia])
5. Negativism (ie, opposition or no response to instructions or external stimuli)
6. Posturing (ie, spontaneous and active maintenance of a posture against gravity)
7. Mannerism (ie, odd, circumstantial caricature of normal actions)
8. Stereotypy (ie, repetitive, abnormally frequent, non-goal-directed movements)
9. Agitation, not influenced by external stimuli
10. Grimacing
11. Echolalia (ie, mimicking another’s speech)
12. Echopraxia (ie, mimicking another’s movements)

### Table IV. Panic attack specifiers listed in DSM-5.

### Table V. Diagnostic criteria for catatonia listed in DSM-5.

at least 3 of the 12 features listed in Table V. Finally, with respect to severity specifiers, a change was made when psychosis is present. While it is known that not all severe mood episodes are psychotic, it is also acknowledged that not all psychotic mood episodes are severe. In DSM-5, there is now an opportunity to indicate psychosis in the absence of high severity.
Other specifiers used in the mood disorder chapters have remained largely unchanged as shown in Table III. Of note, however, the specifier, “with post-partum onset,” has been changed to “with peripartum onset.” This specifier can now be applied to a current major depressive episode or, if full criteria are not met currently, to the most recent major depressive episode if the onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

It is expected that changes to the DSM-5 will be implemented in much less than the 20-year period between DSM-IV and DSM-5. Making appropriate changes to diagnostic criteria and specifiers that capture significant advances in clinical research, including advances in neuroscience and genetics should lead to improved recognition and treatment. It is hoped that such changes will demonstrate the utility of increased use of specifiers and the identification of diagnostic subgroups that can be validated by objective biomarkers.

Dr David Kupfer has the following disclosures:
Consultant to the American Psychiatric Association (as Chair of the DSM-5 Task Force); joint ownership of copyright for the Pittsburgh Sleep Quality Index (PSQI); member of the Valdoxan Advisory Board of Servier International; a stockholder in AlphCorm; and he and his spouse, Dr Ellen Frank are stockholders in Psychiatric Assessments, Inc. Dr Frank also has the following disclosures: received royalties from the American Psychological Association and Guilford Press; member of the Valdoxan Advisory Board of Servier International; Editorial Consultant for the American Psychiatric Press; and has received honoraria from Lundbeck.

References

Keywords: bipolar disorder; depression; diagnostic criteria; DSM-5; specifiers

Dépression et nouvelle classification DSM-5

Le DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5e édition), une mise à jour essentielle de la nomenclature psychiatrique, a été publié l’année dernière, en mai 2013. Cette révision voit le jour après plusieurs années d’efforts interdisciplinaires de plusieurs centaines de scientifiques et de médecins qui ont amélioré la description clinique et les critères diagnostiques de tous les troubles psychiatriques. Premièrement, la prise en compte de l’évolution de la maladie au cours de la vie a fait modifier la structure générale des chapitres et l’ordre de présentation et de description de chaque trouble au sein de chaque chapitre. Deuxièmement, l’évaluation des facteurs spécifiques liés au sexe, à la fois au sein des différents troubles et entre eux, fait l’objet d’une attention particulière. Troisièmement, bien que les précédentes versions du DSM aient abordé les questions culturelles, le DSM-5 les traite de façon spécifique et croisée. Quatrièmement, le système multiaxial de la classification psychiatrique est abandonné et tous les troubles psychiatriques et médicaux sont examinés sur un seul axe. Dans les troubles de l’humeur, le changement le plus évident est celui de la séparation entre les troubles bipolaires et apparentés et les troubles dépressifs s’inscrivant dans des entités individuelles. Le chapitre des troubles dépressifs comprend maintenant huit troubles spécifiques dont le trouble de dérégulation de l’humeur dite explosive, le trouble dépressif majeur (y compris l’épisode dépressif majeur), le trouble dépressif récurrent (dysthymie), le trouble dysphonique prémonstruel, le trouble dépressif induit par une substance ou un médicament, le trouble dépressif dû à une autre affection médicale, les autres troubles dépressifs spécifiés et non spécifiés. Les niveaux de sévérité, d’éventuels sous-types et l’attribution de nombreux indicateurs quand c’est nécessaire font l’objet d’un intérêt plus important. Ces modifications du DSM-5 devraient nous permettre de changer de façon adéquate les critères et indicateurs diagnostiques qui illustrent les avancées significatives de la recherche clinique, y compris celles des neurosciences et de la génétique.
To mark the celebration of 2013 as “France-Vietnam Year” and 2014 as “Vietnam-France Year,” Medicographia looks back on two Alexanders who have become iconic French figures in Vietnam: Alexander of Rhodes, the Jesuit who in 1666 introduced the romanized script still in use in Vietnam today, and Alexandre Yersin, a microbiologist from the Pasteur Institute who in 1894 famously discovered the agent of plague and developed the vaccine against the disease.

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On June 20, 1894, Yersin bribed some English sailors in charge of the hospital mortuary to allow him to excise some buboes from the corpses before burial. Hurrying to his laboratory with the specimens, he made slides and discovered masses of very small, thick bacilli with rounded ends. The bacteria were Gram-negative and exhibited bipolar staining with aniline dyes. He inoculated agar, and the isolates, when injected into mice and rats, produced plague.

Alexandre Yersin: plague, rubber, and cinchona

by J. V. Hirschmann, USA

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Plague has occurred in three pandemics, causing staggering mortality and social disruption. The first began with the Plague of Justinian and lasted from 541 to about 750. The second started in 1346 and ended about 1750. The third, beginning in western China, appeared in Hong Kong in 1894. There, an obscure 30-year-old microbiologist, Alexandre Yersin, who had trained in Paris with Louis Pasteur and Emile Roux, discovered the cause of plague and identified its vector as rats. He developed an effective antiplague serum from injecting plague bacilli into horses. Earlier, Yersin had traveled to the Far East and had conducted four explorations into French Indochina, primarily in Vietnam, mapping the areas and studying their potential for mining, agriculture, and forestry. After his plague studies, he remained in Vietnam, except for brief trips abroad. He developed a laboratory there, planted rubber trees, and sold its latex to the Michelin Company. During World War I he planted cinchona trees to provide Vietnam with its own supply of quinine to combat malaria. He had widespread interests—astronomy, radio, photography, and French automobiles—that he pursued until his death at 77 in 1943.

Medicographia. 2014;36:528-539 (see French abstract on page 539)
Three pandemics of bubonic plague have ravaged mankind, causing horrific mortality and widespread social devastation. The first one began in Egypt with that portion of it known as the “Plague of Justinian” (541-543), so called because it started in the reign and territory of the Eastern Roman Emperor Justinian (482-565) and because he contracted the disease, which he luckily survived. The pandemic eventually spread to Europe and continued as periodic outbreaks until it ended and plague mysteriously vanished in the 8th century.

Of course this did not mean that the disease had disappeared entirely, and arguably one of the most famous early victims of the plague, according to his medieval chroniclers, was king Saint Louis, an icon to French school-children who all recite: “Saint Louis died of the plague in 1270 during the 8th Crusade…” even though it is today recognized that the culprit was most probably dysentery. But plague is more the stuff of legend than dysentery….

Plague returned with ferocity in 1346, probably arising in central Asia, traveling along trade routes, and arriving in Crimea in 1347. From there the second pandemic spread to numerous seaports, such as Messina in Sicily, Venice, Genoa, and Marseille, and then throughout Europe, killing more than one-third of the population in five years.

Physicians during this pandemic used the Latin word pestis ("pestilence" in English) for the disease or "plague," from a Greek word meaning "stroke" or "blow." A common term was the "Great Mortality." Only two centuries later was the illness first called the Black Death, not referring to the dark skin lesions that can occur, but apparently because of a Scandinavian mistranslation from the Latin of atra mors, for in its original source atra meant "terrible," not "black." Despite this error, the outbreak from 1346-1353 has been called the Black Death since. Further epidemics occurred intermittently, but frequently, in the succeeding years, until the second pandemic ended when plague disappeared from Europe in the 18th century. The third pandemic started in western China and spread to Canton and Hong Kong in 1894. Plague then disseminated to other Asian countries, Africa, and, apparently for the first time, to Australia and the Western Hemisphere. Between 1896 and 1910 an estimated 13 million people died in China and India alone.

Throughout these pandemics the clinical description and the human responses to the disease were strikingly similar despite the disparate cultures, countries, and times involved. The illness began suddenly with fever, usually followed shortly by the development in the groin, thigh, axilla, or neck of an excruciatingly painful swelling, called a “bubo” (Greek for “groin”). Sometimes, it drained pus, which was a favorable sign. Cough, dyspnea, and bloody sputum could occur and signified imminent demise. Cutaneous ulcers, carbuncles, or pustules might arise, but black spots (called “God’s tokens” during the Black Death) were especially ominous. Many victims reeked from the stench of their breath or because of putrid discharges from their sores or nasal cavities. Some became delirious or comatose. Death usually arrived within a few days, but it could be sudden. In Constantinople in 542, for example, people wore nametags for identification in case they should abruptly fall dead in the streets. Plague during pregnancy was particularly lethal. The overall case-fatality rate in the first two pandemics is impossible to determine, but among untreated patients in the third pandemic it ranged from about 40% to 80%. Its source was puzzling. A common explanation in most cultures—including Christian, Moslem, or Chinese—was that it be sudden. In Constantinople in 542, for example, people wore nametags for identification in case they should abruptly fall dead in the streets. Plague during pregnancy was particularly lethal. The overall case-fatality rate in the first two pandemics is impossible to determine, but among untreated patients in the third pandemic it ranged from about 40% to 80%. Its source was puzzling. A common explanation in most cultures—including Christian, Moslem, or Chinese—was that it...
was God’s vengeance for widespread human depravity. Some thought that it resulted from “miasma,” air polluted by noxious substances that could enter the human body through the skin or respiratory tract. A third concept was that it arose from a malign configuration of the planets. These three explanations often overlapped, as when Shakespeare alluded to “a planetary plague, when Jove/Will o’er some high-viced [ie, vice-ridden] city hang his poison/in the sick air” (Timon of Athens IV; iii: 110-112). Although the mechanisms were unclear, the disease seemed contagious, and a common response was to avoid the sick. One option, especially for the wealthy, was to flee. In The Decameron by Giovanni Boccaccio (1313-75), for example, the ten fictional characters abandon plague-infested Florence in 1348 to travel into the surrounding countryside, where they entertain themselves by telling ten stories daily for ten days. Many physicians approved: a late 15th-century German manuscript stated, “Clever doctors have three golden rules to keep us safe from pestilence: get out quickly, go a long way away, and don’t be in a hurry to come back.” “[Flüch bald, flüch ferr, kom spät herein, dann fürvar das sind drei nützere Krüter,” from the Büchlein der Ordnung der Pestilenz (1473), by Heinrich Steinhöwel, town doctor of Ulm from 1450 to 1482]. Because plague was also present in rural areas, however, traveling there did not necessarily avert infection. Indeed, evidence of widespread plague deaths was often apparent—farms deserted, crops abandoned, livestock unattended.

A second response to the fear of contagion was the ruthless desertion of the afflicted by friends and families, who sometimes paid others to attend their sick relatives and bury them when they died. Another reaction was to isolate the ill. In some places guards were placed outside their dwellings to keep them incarcerated. In the London epidemic of 1665, Samuel Pepys (1633-1703) recorded in his diary how the doors of those houses were marked with a red cross and the words “Lord have mercy upon us.” Such imprisonment seemed inhumane: “This disease makes us more cruel to one another than if we are dogs.” In Germany, houses of inhabitants with the plague were marked with black crosses, and the word “Pest” (plague).

Another attempt at preventing disease was to exclude potentially contagious outsiders from entering a community. For example, in 1383 travelers to Marseille and their goods were sequestered for 40 days (“quarantine” in Italian) before receiving permission to come into the city. The result of the staggering death rates, isolation of the sick, and flight from urban areas was that the streets of even large cities were largely deserted. Deserted, that is, of live bodies, but not necessarily dead ones, whose number and stench were overwhelming. Disposal of the corpses was challenging. Numerous accounts concur with Boccaccio’s description: “When all the graves were full, enormous trenches were dug… into which the new arrivals were put by the hundreds, stowed layer upon layer like merchandise in ships….”

The traditional rituals surrounding death were commonly abandoned or curtailed. The historian Procopius (500-565), who was in Constantinople when the plague struck in 542, wrote, “All the customary rites of burial were overlooked… it was sufficient if one carried… the body of one of the dead to the parts of the city which bordered on the sea and flung him down; and there the corpses would be thrown upon skiffs in a heap, to be conveyed wherever it might chance.”

The plague had other effects on human behavior. Procopius described how some previously licentious people became suddenly religious…until the danger passed and they returned to their prior villainy. Boccaccio wrote that many lived moderately and abstemiously, but others “maintained that the surest medicine for such an evil disease was to drink heavily, enjoy life’s pleasures…satisfying their appetites by any means available….” Searching for causes, some blamed the disease on others. Accused of poisoning wells and rivers, nearly 1000 Jews were burned in Strasbourg in 1349, and other Jewish communities in the Rhineland were almost completely annihilated. At about the same time, flagellants, condemning them-
Alexandre Yersin (1863-1943) was born in a Swiss village on the shores of Lake Geneva, three weeks after his father’s death. His 25-year-old mother moved her children to the nearby town of Morges, where she started a finishing school for girls that emphasized household skills and elegant French manners. Yersin, who was quite misogynistic, regarded the girls with contempt, but he did remain close to his mother and his sister, writing nearly 1000 letters to them until their deaths in 1905 and 1933, respectively. In 1883, he began his medical studies in Lausanne, but after one year went to Marburg Germany. In 1885, he transferred his medical education to Paris, where he became a student at Hôtel-Dieu, a large public hospital dedicated to treating the poor. Shy, solitary, and intensely private, Yersin found himself more interested in pathology than patient care. He began work in the laboratory of the eminent pathologist Andre Cornil (1837-1908), where he translated German articles for the Professor and performed dissections, including autopsies of rabies victims. After meeting Emile Roux and Pierre Petit, he decided to become a career in microbiology: “Scientific research is very interesting, but Mr Pasteur is quite right when he said that, unless he is a genius, a man must be wealthy to work in a laboratory and risk leading a miserable existence, even if it does win him a certain scientific renown.” Accordingly, he became a ship’s doctor, initially traveling between Saigon and Manila. He learned Vietnamese in order to communicate with the crew, and to allay the monotony of his trips, he also studied navigation and cartography. After a year, he began sailing between Saigon and Haiphong along the coast of Vietnam. It was then part of French Indochina, formed in 1887 as a federation of three Vietnamese regions—Tonkin in the North, Annam in the Central area, and Cochin China in the South—as well as Cambodia, with Laos being annexed in 1893. Recognizing that no European had visited much of this territory, he conducted four explorations into the interior from 1891-1894. Although small in stature, he possessed the extraordinary stamina and tenacity required to confront the challenges of these hazardous and physically demanding journeys. Travel was often on foot, and he had to contend with rugged terrain, heat, rain, leeches, tigers, mosquitoes, tropical diseases, and, sometimes, unscrupulous guides and interpreters. He also encountered hostility from some village chiefs, who denied passage through their territories. He took chronometers, altimeters, and compasses to map the areas and wrote detailed notes about the geography, flora, fauna, and people seen along the way. From these experiences, he made recommendations for road building, mining, and agriculture.

His first trip, in July 1891, was an ambitious attempt to journey from the coast southwest across the Annamite mountain range to Saigon 500 km away. Travelling through heavy rain, he only reached the plateau of Djiring, where he first met
Saigon to explore the southern part of the Central Highlands, heading northeast and discovering along the way the fertile plateau of Lang Bian. Admiring its tall trees, lakes, waterfalls, and temperate climate, he recommended building a holiday resort there for French civil servants. The result was the charming village of Dalat, which also became a source of vegetables and fruits for the Vietnamese lowlands.

Other major accomplishments during this trip were developing accurate maps, including the height and configuration of its mountains; recording the customs of its inhabitants; and calculating its potential for commerce, livestock, mining, and forestry. In June, he caught up with some escaped prisoners and their five rebel chiefs, whom he fought alone, sustaining a saber wound to his right hand and the blow of a rifle butt to his right leg that incapacitated him for several days. When the main rebel chief was later arrested, Yersin witnessed his execution, admiring the impassivity of the victim, who sustained four blows with a sword before decapitation finally occurred.

His last exploration was a three-month trip in 1894 from the sea westward to the Central Highlands, following a varying northward course that finally ended at the coast in Da Nang. This time he had guards accompany him. Once again, he made detailed geographic observations and accurate maps of the significant villages and landmarks, but had to abandon nearly all his equipment because of unspecified difficulties.

the Montagnards, the inhabitants of the Vietnam highlands. Suffering from a severe attack of malaria and unable to find further guides, he abandoned his trip, returning to the coast disheveled, his feet bare and bleeding.

Albert Calmette (1863-1933), later famous for developing a vaccine against tuberculosis (Bacillus-Calmette-Guerin [BCG]), had been sent from the Pasteur Institute in Paris to found a branch in Saigon. He persuaded Yersin to join the French Colonial Health Service, which, he argued, would help support further explorations. In March 1892, Yersin began an officially authorized trip of three months from the coast at Nha Trang—a region he was to fall in love with and settle at permanently—west through the Central Highlands into Cambodia, reaching the Mekong River. His interpreter stole a large share of his goods and deserted. Yersin then traveled south on a river boat to Phnom Penh before returning to Saigon. During his trip, he mapped the area around the Mekong River, made observations about the natives, and took many illuminating photographs. Quinine prevented malaria, but he suffered a severe attack of dysentery.

In October 1892, Yersin returned to Paris, where, with Pasteur’s help, he obtained funding for his next expedition. In February 1893, he began a seven-month trip from Saigon to explore the southern part of the Central Highlands, heading northeast and discovering along the way the fertile plateau of Lang Bian. Admiring its tall trees, lakes, waterfalls, and temperate climate, he recommended building a holiday resort there for French civil servants. The result was the charming village of Dalat, which also became a source of vegetables and fruits for the Vietnamese lowlands.

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The Bay of Nha Trang, at the turn of the 19th century. All rights reserved.

Military doctors at the Saigon Hospital, in 1893. Yersin is the first from left, back row (his name is written over his white uniform jacket). Albert Calmette is seated, first from left, front row. © Institut Pasteur.
After Yersin returned, Calmette asked him to travel to the British colony of Hong Kong to investigate the outbreak of plague there, which heralded the third pandemic. He arrived on June 15, 1894, with a staff of only two untrained people, one who quickly absconded with Yersin’s money. Yersin’s only equipment was a microscope, an autoclave, and culture supplies. His arrival in Hong Kong was three days after that of Shibasaburo Kitasato (1852-1931), whom the Japanese government had sent to investigate the epidemic as well. Kitasato was a famed microbiologist who spent seven years in Robert Koch’s Berlin laboratory, where he developed anaerobic techniques that allowed him to isolate the cause of tetanus (Clostridium tetani) in pure culture for the first time. In addition, he discovered and characterized its exotoxin and, with Emil Behring (1854-1917), produced tetanus antitoxin. Kitasato came to Hong Kong with six assistants and received gracious hospitality from the Scottish doctor James Lowson (1866-1935), who was Superintendent of the Government Civil Hospital. He provided Kitasato with laboratories and facilities for autopsies. On June 14, Kitasato detected a bacillus in postmortem specimens. He inoculated a mouse and saw a similar bacterium in another patient. Lowson was confident Kitasato had found the cause of plague and wired the British journal *Lancet* with that claim.

Lowson was less enthusiastic about Yersin, who was unprepossessing, unable to speak English, shy, and, in contrast to Kitasato, unrenowned. Lowson refused Yersin access to autopsies. Yersin did manage to get a straw-covered bamboo hut constructed on the grounds of a recently converted hospital, where he established his laboratory. On June 20, at the advice of an Italian missionary, he bribed some English sailors in charge of the hospital mortuary to allow him to excise some buboes from the corpses before burial. Hurrying to his laboratory with the specimens, he made slides and discovered masses of very small, thick bacilli with rounded ends. The bacteria were Gram-negative and exhibited bipolar staining with aniline dyes. He inoculated agar, and the isolates, when injected into mice and rats, produced plague. On June 23, he demonstrated that rats dying in the streets of Hong Kong, like humans, had buboes filled with enormous numbers of the same bacilli. Yersin concluded that rats were the principal vector of plague.

Although Yersin clearly identified the plague bacillus, Kitasato had apparently discovered it six days earlier. The slides that Lowson and Kitasato sent to the *Lancet* and *British Medical Journal*, however, seemed to show two organisms: small bacilli, but also diplococci. Moreover, Kitasato was unable to state whether the bacillus was Gram-positive or Gram-negative, and he erroneously suggested that it was slightly motile. A probable explanation for Kitasato’s confusing initial reports is that another bacterium, possibly *Streptococcus pneumoniae*, contaminated his cultures. The question of priority for first finding the cause of plague generated considerable controversy, exacerbated by false claims and contradictory statements that Kitasato and his colleagues made afterwards, with Kitasato sometimes insisting that the microbe that he identified was different from Yersin’s isolate. The definitive resolution of this debate is reflected by the nomenclature of the plague bacillus. It was called *Bacterium pestis* before 1900, *Bacillus pestis* until 1923, and *Pasteurella pestis* up to 1970, when it received its final name, *Yersinia pestis*. 
Yersinia pestis, discovered by Yersin during the Hong Kong plague epidemic in 1894. © Institut Pasteur.
Yersin’s involvement with plague did not end with discovering its cause. In 1896, he was back in Paris working with Calmette on an antiplague serum obtained by injecting bacilli into horses. He returned to Nha Trang later that year, and when plague recurred in 1896, he tried the therapy on an 18-year-old Chinese seminary student on June 26. It was the first recorded use of antiplague serum, and the patient survived, as did 21 of 23 other victims who received his remaining supply. Soon, he set up serum production in Nha Trang, where he built another Pasteur Institute, comprising a hospital, vaccination center, laboratory, and observatory. He lived there most of the remainder of his life. In 1897, plague erupted in India, and Yersin introduced his treatment there. Yersin’s antiserum and other similar formulations, employed until the advent of antimicrobial agents, reduced the mortality rate of plague from about 80% to about 35%. With streptomycin use, beginning in 1947, it was about 5% to 10%, which remains the current rate with gentamicin or doxycycline therapy.

Yersin had always been ambivalent about medical practice. In a letter, he wrote: “I take great pleasure in treating those who come to me, but I should not like to make medicine my living. I could never ask a patient to pay me for the treatment…. I regard medicine as a sacerdotal office, like the priesthood. Demanding payment for treating an invalid is rather like saying, ‘Your money or your life.’” Accordingly, after his work with plague, he became involved in other pursuits. In 1899, he established the first nursery for rubber trees in Vietnam, having imported the plants from Brazil, and he sold the first collection of latex to the Michelin Company in 1904. Asked by the French government to help found a medical school in Hanoi, he acted as its director from 1902-1904. He was appointed as the overall director of the Pasteur Institutes in Indochina. In 1915, after the outbreak of World War I, he determined to have Indochina make its own quinine, which comes from the bark of cinchona trees. Finding the appropriate growing conditions was challenging, but, using seeds that he had acquired in Java, his efforts eventually succeeded.

In 1919, he became Inspector of the Pasteur Institutes of Indochina and in 1923, received the honorary title of Inspector General upon his retirement. He became interested in astronomy, radio, photography, and French automobiles, buying successive models, which he drove in Vietnam. In 1933, he was appointed a member of the Scientific Council of the Pasteur Institute in Paris, where he traveled annually to attend its meetings. On May 30, 1940, at the end of his last visit, he took a midnight plane destined for Saigon just six hours before the invading German army closed the Paris airport. Back in Nha Trang, where he witnessed the Japanese occupation of Indochina, he died peacefully on February 27, 1943, at the age of seventy-seven. On his tombstone is the inscription, “Benefactor and humanist, venerated by the Vietnamese people.” Indeed, he remains renowned in Vietnam, where streets

Yersin’s house and the cupola of his observatory, in Nha Trang. © Institut Pasteur – Musée Pasteur.
bear his name, his burial site is honored, and his dwelling in Nha Trang is a museum. The Linh Son Phap Pagoda, in the village of Suôi Cat, some 20 km from the Nha Trang Bay, contains a shrine to Yersin, with his portrait, the object of a fervent cult.

Yersin’s discovery of the plague bacillus and its presence in rats left several issues unanswered. It was unclear how rats or humans acquired the bacteria. Paul-Louis Simond (1858-1947), another Pasteur-trained microbiologist, noticed that people could safely handle rats that had died of the plague several hours earlier, but not when the animals had just expired. He proposed that there must be an intermediary between the rat and humans, suggesting the rat flea (*Xenopsylla cheopis*) as the culprit. When a rat corpse cools, the fleas seek another warm-bodied animal, preferably another rat, but if none is available, humans suffice. While studying the disease in India, he found plague bacilli in the intestines of fleas from infected rats, but not in those from healthy ones. Simond placed a rat suffering from plague into a jar and housed a healthy one above him on a screen, close enough for fleas to jump, but far enough to avoid direct contact between the animals. The healthy rat contracted plague. When a rat with plague, but no fleas, was similarly housed with healthy rats, no infection occurred. When fleas were added, however, plague developed. Subsequent studies, many conducted by the Indian Plague Commission formed in 1905 and comprising both British and Indian investigators, resolved several others issues about the source and transmission of plague. *Y pestis* enters *X cheopis* when it sucks blood from infected rats, which have high-level bacteremia. When they next feed, infected fleas regurgitate the bacteria into the bite site, transmitting the bacilli to a new host.

Foci of plague currently exist in all continents except Australia and Antarctica. The reservoir for the organism is a chronic carrier state in various wild rodents—such as gerbils, marmots, field mice, and ground squirrels—which, unlike rats, remain relatively healthy despite prolonged bacteremia. These mammals typically acquire *Y pestis* through bites from fleas, including species other than *X cheopis*. *Y pestis*, however, can also survive for months in soil, which, if contaminated, could cause infection when rodents inhale or ingest it. Modern observations have confirmed the clinical features described in the earlier pandemics. Disease occurs primarily in three forms: 1) bubonic plague, with fever and swollen, tender, necrotic, and hemorrhagic lymph nodes; 2) septicemic plague, in which bacteremia occurs, but no bubo develops; 3) pneumonic plague, either as a complication of bacteremia or from inhalation of aerosolized bacteria from people with plague pneumonia or from respiratory secretions of infected mammals.

In addition to transmission via fleas and inhalation of *Y pestis*, plague can occur from direct handling of infected animal tissues or by ingesting the organism. The incubation period is 2-10 days, and in the bubonic form *Y pestis* travels from site of inoculation to the regional lymph nodes, where buboes form. The pus-tules, carbuncles, and ulcers described in older accounts were probably infection by *Y pestis* at the site of the flea bite. The ominous black spots (“tokens”) may also have been primary infections, but some were probably cutaneous hemorrhages and gangrene produced by disseminated intravascular coagulation. Finally, studies of DNA isolated from the teeth of plague victims in ancient grave sites have demonstrated that the first two pandemics were indeed caused by *Y pestis*, although they appear to be from different strains. These investigations confirm that the tiny bacillus that Alexandre Yersin discovered has, over many centuries, killed tens of millions of people, making it the most lethal bacterium in human history.

![Xenopsylla cheopis](image)
Further reading


ALEXANDRE YERSIN : PESTE, CAOUTCHOUC ET QUINQUINA

La peste, à l’origine de trois pandémies, fut responsable d’une mortalité effroyable ainsi que d’intenses bouleversements sociaux. La première pandémie débuta en 541 sous l’empereur Justinien pour se terminer aux alentours de 750. La deuxième, désignée plus tard sous le nom de Peste Noire, sévit de 1346 à 1750. La troisième toucha la Chine occidentale, faisant son apparition à Hong Kong en 1894. C’est là qu’un obscur microbiologiste de 30 ans, Alexandre Yersin, élève de Louis Pasteur et d’Émile Roux à Paris, découvrit l’agent responsable de la peste et attribua le rôle de vecteur au rat (le vecteur immédiat, la puce, ne fut identifié que plus tard par un autre pasteurien, Paul-Louis Simond). Yersin mit au point un sérum efficace contre la peste en injectant des bacilles pesteux au cheval. Auparavant, Yersin avait effectué des voyages en Extrême-Orient et mené quatre campagnes d’exploration en Indochine française, principalement au Vietnam, établissant une cartographie des régions traversées et déterminant leur potentiel minier, agricole et selvaticque. Après ses études sur la peste il s’établit définitivement (hormis quelques brefs voyages à l’étranger) au Vietnam. Il y fonda un laboratoire, créa des plantations d’hévéas (arbres à caoutchouc) et devint le fournisseur des usines Michelin. Pendant la Première Guerre Mondiale Yersin se lança dans la plantation de quinquina (Cinchona officinalis) afin d’assurer une ressource autochtone de quinine pour combattre le paludisme. Yersin s’intéressait à de nombreux domaines dont l’astronomie, la radiophonie, la photographie, et sa collection d’automobiles de fabrication française, toutes passions qu’il entretint jusqu’à sa mort, intervenue à l’âge de 77 ans, en 1943.
Portrait of Alexander of Rhodes
(Avignon, 15 March 1591–Estahan 5 November 1660).
Oil on canvas. © Fonds Iconographique des Archives Missions Étrangères de Paris. With kind permission.
Simpler to learn than the two other scripts based on Sino-Vietnamese characters, Alexander of Rhodes’ quôc ngu romanization was to become a tool in the democratization of education, which, in spite of its Western and Catholic origin, was adopted in 1954 as the official Vietnamese administrative writing system, replacing Chinese, which had been kept as the language of the imperial administration by the French colonial power.

Alexander of Rhodes: hyperpolyglot* missionary and father of the modern Vietnamese alphabet

by F. Fauconnet-Buzelin, France

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The signing of the 1954 Geneva accords brought to an end the First Indochina War, and with it nearly a century of French domination of the ancient Đại Việt empire. The new Vietnamese administration abandoned the use of Chinese characters and adopted quôc ngu, a transcription into the Latin alphabet of the local language. Invented in the 17th century, quôc ngu was the work of a small group of Jesuits one of whom has emerged as a major figure in the history of Vietnam: Alexander of Rhodes. It would be hard to find a more cosmopolitan missionary than this descendant of a family of Aragonese Marranos (Christianized Jews of medieval Spain) who sought refuge in 15th-century Avignon, then a papal enclave. Italian on his mother's side, French and Provençal in language and culture, Alexander of Rhodes was, however, listed as a subject of the Pope in the public records. After studying in Rome for ten years, he spent time in India, China, Cochin China, and Tonkin, before returning to Rome and then Paris, after which he left for Persia, where he lived out his last six years. His itinerant life and singular linguistic ability meant that Rhodes became a walking dictionary who spoke over a dozen languages, including Latin and Hindustani, Hebrew and Chinese, not to mention Greek, Portuguese, Provençal, Konkani, Japanese, Vietnamese, and Italian. His lasting fame is attached to his linguistic work on the Vietnamese language, but Rhodes was also a great missionary who played a central part in the early evangelization of Vietnam, and in the reform undertaken by the Vatican in the 17th century to free young Christian communities in Asia from the colonial stranglehold of Portugal.

Medicographia. 2014;36:540-550 (see French abstract on page 550)
The call of the Orient

Alexander of Rhodes was born on 15 March 1591 into a family of Jewish origin, which, fleeing the horrors of the Spanish Inquisition, had found refuge at Avignon, the papal city that had welcomed Jews since the mid-14th-century reign of Pope Clement VI. Converted to Catholicism, the Rhodes family acquired a certain affluence through the silk trade and so could offer the best education to the young Alexander, who studied at Avignon’s Jesuit college, where he had as teacher the great geographer Father Gabriel Bonvalot.

His reading of the famous missionary Relations (the Jesuit letters from Japan, China, etc, which they wrote to their Superiors in Europe as accounts of their missionary work, brimming with fascinating details of their discoveries of “exotic” countries, cultures, and mores), the best recruitment tool of the burgeoning Society of Jesus, crystallized his missionary vocation and spurred him to join. These Relations at the time focused on the young Christian community in Japan, where the dazzling success of Francis Xavier and his successors since the end of the 16th century was soon to give way to persecutions. Fired by these accounts, Alexander asked to be received at the Jesuit novitiate in Rome so he could “leave Europe and its delights for the salvation of the Japanese, the Chinese, or any others.” After six years in the Eternal City, from 1612 to 1618, he was sent to Lisbon, the point of departure to Asia for missionaries. The Kings of Spain and Portugal provided transport and support for the missionaries, and in exchange had exercised tight control over their activities through the Padroado (see box) since the 1494 Treaty of Tordesillas they had signed with the Vatican. This treaty ended colonial rivalry between the two Iberian sovereigns, following the age of discovery, by dividing the world in two: the Americas, with the exception of Brazil, coming under the control of Spain, and Asia, apart from the Philippines, under the aegis of Portugal.

Missionary and linguistic achievements in Vietnam

Alexander of Rhodes was appointed to the mission in Japan, in accordance with his wishes. After a journey of almost four years, two of them spent in Goa, the capital of the Portuguese Indies, and nine months in Malacca, in May 1623, he reached Macau, the great trading post “rented out” by the Portuguese to the Emperor of China. Macau was also the hub of the Far East missions, and it was here that Rhodes experienced his greatest disappointment when he learned that because of worsening persecution in Japan no new missionaries were to be sent there. And a few months later, in February 1624, the shogun (military governor) Hideyoshi issued an order banning
all missionaries, thus dashing any lingering hopes Rhodes had of reaching the Japanese archipelago. Instead, his superiors instructed him to leave for a new mission, in Cochin China. Cochin China and its capital Hue at the time formed the southern part of the Đạỉ Việt Kingdom, where the Emperor Lê held no more than symbolic sway over a country divided between two rival clans, the Trịnh reigning over Tonkin, in the North, and the Nguyên over Cochin China, in the South. Since the 16th century, the ships of Portuguese traders had plied back and forth between Macau and the great Cochin Chinese port of Tourane. King Sai Vuong (1562-1635; Nguyên dynasty) it seems took a favorable view of these foreigners, who brought to his country Chinese porcelain, tea, lead, silver, copper, saltpeter, weapons, and cloths, and to whom he could sell silks, spices, herbs, and rice. Taking advantage of the sovereign's warm welcome, the Jesuits Francesco Buzomi and Diego Carvalho had set up a mission at Tourane in 1615. In 1624, Macau sent them six new missionaries, one of whom, Alexander of Rhodes, would soon make his mark.

From the outset it was clear that Rhodes stood out, not so much because of his zeal, as many of his fellow Jesuits shared this fervor, but rather through the extraordinary facility with which he learned the local language, which on his arrival he likened to the “chirping of birds.” In three weeks he learned the pronunciation and tones, the great difficulty of Vietnamese, from a 12-year-old boy, whom he instructed in Portuguese and Latin and who became his assistant and practically his adoptive son, as witnessed by the name the boy took—Raphael of Rhodes. Just six months later, Rhodes was preaching in Vietnamese and, winning over his congregation as much by his apostolic enthusiasm as his meridional volubility, made numerous conversions at Faifo and Tourane. And even at Hue, where he baptized a close relation of the King whom he named Mary Magdalene and who became a fervent champion of Christianity.

Success breeds opposition
This craze for a new religion, which ran counter to the social and religious customs of the Vietnamese, in particular ancestor worship, naturally stoked opposition from the King’s courtiers and from religious leaders who lost no time in pointing the finger at the missionaries whenever a natural disaster struck. King Sai Vuong, essentially concerned with national prosperity, left the missionaries to their own devices as long as business thrived, but was more exacting when trade declined. In 1625, when no Portuguese ship anchored in the port of Tourane, the displeased king confined the Jesuits to Faifo. Restricted in their movements in the country’s interior, the missionaries had to travel often to Macau for gifts to allay,...
Building up a dedicated corps of indigenous catechists

Then at war against his Cochin-Chinese neighbor, local lord Trinh Trang agreed to receive the newcomers at Cua-Bang, to see what advantages he could extract from them. Rhodes seized the opportunity to seek favors through the gift of an hourglass. Trinh Trang invited him to reside in Hanoi, in a fine wooden house part of which was transformed into a church in which Rhodes preached up to six times a day. Neophytes flocked to the church and Rhodes reported to his superiors twelve hundred baptisms in the first year, two thousand in the second, and three thousand five hundred in the third. Even if the albeit fleetingly, royal resentment. Rhodes strained at the leash and overcame his boredom by improving the romanization of the Vietnamese language initiated by his colleagues Francisco de Pina, Gaspar do Amaral, and Antonio Barbosa.

In 1626, Rhodes was recalled to Macau, as his linguistic talents were needed elsewhere. Another Jesuit, Giuliano Baldinotti, recently arrived in Tonkin, had used his mathematical knowledge to curry favor with Trinh Trang, the chua or local lord (1577-1654; Trinh dynasty). However, he spoke no Vietnamese and asked his superiors to send someone able to converse with Trinh Trang and thereby to reap the benefits of what he had sown. Alexander of Rhodes was just the man for this situation. On 19 March 1627, he arrived at Cua-Bang, in the province of Thanh-Hoa, accompanied by a Portuguese Jesuit who had been in Japan, Pedro Marquez, whose task it was to minister to Japanese Christians who had sought refuge in Tonkin. Baldinotti had just been expelled because of his strong opposition to ancestor worship, toward which Rhodes, in contrast, had always shown remarkable tolerance, considering most ceremonies celebrated in honor of the dead as “quite harmless.” Even before disembarking at Tonkin, from the vantage point of the ship’s rail Rhodes held forth to the crowd below that had gathered to inspect the ship’s cargo, praising the merits “of another merchandise” that he “offered for free and which was the true law and the path to happiness.” Won over, two “very wise” people asked to be baptized there and then.
accuracy of these figures may perhaps be questioned, given Rhodes’s Latin temperament and tendency to exaggerate and the common practice of the Jesuits of the time to inflate numbers, they nonetheless give some idea of the extraordinary persuasiveness he had acquired after only three years in Vietnam. Spurred by Rhodes’s enthusiasm, fascination for the new religion reached Trinh Trang’s entourage, and his sister as well as seventeen of his relatives asked to be baptized. To tackle the huge workload engendered by this rising demand, Rhodes recruited among new converts the most fervent and best trained catechists who were preparing the catechumens for baptism. After vowing celibacy and fidelity to the Fathers of the Society of Jesus and sharing their worldly possessions, these itinerant catechists, with their rudimentary training in medicine, became indispensable to the Vietnamese Christian church. They ensured the survival of communities when the missionaries had to leave the country, which was happening increasingly often.

Needless to say, Rhodes’s conspicuous success worried those whose position was threatened by the principles of the new belief: the royal concubines, fearing that Trinh Trang, if he were to convert to Christianity, would be obliged to adopt monogamy; the eunuchs, the seraglio guards, fearful of a threat to their livelihood; and the religious notables, who foresaw a dwindling of followers. The concubines accused the foreigners of secret dealings with Cochin China, the enemy in the South (had not Alexander of Rhodes come from there?). And the religious notables threatened their people with the wrath of Heaven as a reprisal for the destruction of idols. And the “water of life” of the baptism, which the missionary poured indiscriminately over the foreheads of all dying children that came within his grasp (an absolute condition of eternal salvation in the Christian mind of the time), was soon viewed by some as the “water of death” that finished off the unfortunates.

**Expelled!**

Unable to resist forever the pressure of his entourage, Trinh Trang distanced himself from the missionaries. First he placed Rhodes under house arrest, and then banished him in January 1630. This in no way dampened Rhodes’s apostolic zeal. He even succeeded in converting the captain and twenty-four of the crew of the ship taking him into exile. Having managed to disembark at Ca Chua, the last port in southern Vietnam, Rhodes made a last-ditch attempt to stay on and reached Hanoi aboard a Portuguese ship. But his sermons lasted only
as long as the trade negotiations. Refused an audience with Trinh Trang, Rhodes had to leave Tonkin for good, together with those who had brought him there.

Ten years of purgatory followed. Based in Macau where he taught theology in the town’s school, Rhodes was appointed to care for the small Chinese community. But as he was unfamiliar with their language, he had to preach through an interpreter, which greatly reduced his pastoral influence. Over this decade he baptized just one thousand people in the region of Canton, that is, ten to thirty times fewer than he had managed in Tonkin.

In Cochin China, however, the Jesuits were in an awkward situation. In 1635, Thuong Vuong (1601-1648; Nguyen dynasty) succeeded his father as king and pursued the same ambiguous policy allying mistrust of the foreigners’ religion and interest in the trade opportunities they offered. But Dutch Protestants, the emerging economic power in Asia since they had set up in Batavia (today’s Jakarta, in Indonesia), succeeded in persuading the king that the Catholic missionaries were preparing the ground for a military conquest of his country, instigated by the Portuguese, and Thuong Vuong banished all religious figures in 1639. The Society of Jesus though was not in the habit of giving up, except in the realm of the impossible, as in Japan, and in Macau it was deemed that Rhodes should bring to bear his mastery of the language and his interpersonal skills to regain influence there, a task fraught with difficulty.

Rhodes, accompanied by another Jesuit, Pierre Alberto, arrived at Faifo in January 1640, aboard a Portuguese trading ship. Seven months later they were compelled to return to sea, this time at the helm themselves. After two months of respite in Macau, Rhodes left for Cochin China at Christmas and for half a year visited the Christian communities in the southern provinces. But once more he was spotted and put aboard a ship bound for Manila. From there he sailed for Macau, arriving in September 1641 after almost coming to grief in a storm. His new attempt to return to Cochin China the following year had a rather happier outcome. With armfuls of gifts for Thuong Vuong, he was received at Hue, where he spent his days conversing with the king on scientific subjects and his nights ministering to the Christian community. But royal tolerance was short-lived and Rhodes decided it was wise to return to Macau. Since the outset this had been the Jesuits’ strategy for winning over local powers: kindle interest, win the king’s favor with gifts, withdraw when his interest flags.
Rhodes' last sojourn in Cochin China, between January 1644 and July 1645, went badly wrong. Emboldened by a warm welcome from Thuong Vuong, he unwisely multiplied baptisms (more than two hundred one night in Hue), which fueled the animosity of his detractors who accused him of plotting with the king's aunt, Mary Magdalene, to seize the throne for her descendants. Rhodes was absent when his home was searched, but the police arrested one of his young catechists, André, who was condemned to death and decapitated on 26 July 1645. André was the first of many Vietnamese martyrs. Rhodes, who in vain tried to prevent the execution, was imprisoned for two months and condemned to death, but finally pardoned on the intervention of an advisor whose wife was Christian. He was instead banished and forbidden ever to return to Vietnam, the country he loved, where his voice had swayed so many.

The Paris Foreign Missions Society: from colonialism to evangelization

Now available for other tasks, Rhodes was sent to Rome to plead the cause of the Asian missions, that is, to recruit missionaries. But the dramatic turn of events in Cochin China, so tragically redolent of events in Japan some decades before, had convinced Rhodes that local Asian Christians would be in danger of persecution as long as they were seen to be allies of, or to collude with, foreigners, to wit Western missionaries whose links with the ambitions of European powers were all too plain. To sidestep these perceptions stemming from the system of patronage and to limit persecutions, there was just one solution—train local priests who would blend into the population and favor calmer integration of Christians into their own society. Rhodes, although answerable to the Padroado as a Jesuit, was a papal subject and as such less sensitive than his compatriots to defending Portuguese interests. He was more in line with the new orientations of the Congregation for the Propagation of the Faith, overseer of the missionary policy of the Holy See, which was seeking to withdraw the missions from Iberian supervision. Thus began for Rhodes protracted and thorny diplomatic toing and froing between Rome and Paris, which, in the end, led to the triumph of his ideas and, despite intrigues and pitfalls of all kinds, to the appointment, in 1658, of three French vicars apostolic for Tonkin, Cochin China, and China: Monsignors Pallu, Pierre Lambert de la Motte, and Ignace Cotolendi. Although Rome was mistrustful of the furia francese, there was no other solution because France then was the only Catholic power without interests in Asia, and was home to great spiritual and missionary fervor. Of the three prelates appointed, only Monsignor Lambert de la Motte was able to set foot in Vietnam, in Tonkin (1669), and then in Cochin China (1671 and 1674). It was among catechists instituted by Rhodes that de la Motte recruited the first seven priests in Tonkin. Ordained in January 1670, they constituted the beginnings of a Vietnamese clergy that won renown for its bravura and spirit of resistance over the following centuries.

In the eyes of history it was paradoxically a Jesuit of the Portuguese Padroado, Alexander of Rhodes, who played the leading role in the creation of the Paris Foreign Mission Society (Société des Missions Étrangères de Paris), which posted French secular priests to the Asia missions, deemed to have been founded by Monsignors Pallu and Lambert de la Motte, the first vicars apostolic of Vietnam. Over the three centuries that followed, numerous French priests and bishops of the Foreign Mission Society exercised their ministry in Vietnam, and suffered alongside the Catholic Vietnamese the ordeal of persecutions that resulted in the deaths of thousands. Pope John Paul II canonized 117 of the victims (including ten French priests) in 1988. From the end of the 19th century, these missionaries were confronted by the ambiguities of their own country’s colonization of Indochina, and then faced the hardships of the wars of independence until 1975, when the last of them were expelled from South Vietnam.

Relocation and death in Persia

Despite his pastoral and cultural influence, which is on a par with Francis Xavier’s in Japan and Matteo Ricci’s in China, Alexander of Rhodes did not in his lifetime win just recogni-
tion for his indefatigable zeal in the service of Vietnam and his Church. Quite the contrary. The Portuguese crown, jealous of its patronage rights, took a very dim view of Rhodes’s initiative to introduce Frenchmen, who depended on the Pope alone, into territories it considered its preserve. Until then, the laws of the Padroado and the close links between the young Society of Jesus and the Portuguese monarchs had meant that Lisbon exercised total control over all Jesuits leaving for the Orient aboard its boats, whether they were Portuguese, Italian, French, or even papal subjects, like Alexander of Rhodes. In an attempt to stymie this new missionary enterprise, which was eroding his power, the King of Portugal agreed to fund the departure to Asia of twenty-five new Jesuits, eleven of them French, eleven Portuguese, and three Italians. But not Rhodes, who thus paid the price for his commitment to the service of the Christian community of Vietnam, where he had been the most successful apostle. Blacklisted by the Padroado, sent by his superiors to Persia, Rhodes left in 1654, too soon to witness the fruits of his own endeavors.

It was a cruel relegation, to a country so different from all those he had known, and where conversions were virtually impossible. When he reached the capital Esfahan, at the age of sixty-four, Rhodes set about learning Persian (his thirteenth language!) and wrote notes about the new country of his mission which enabled one of his colleagues, Jacques de Ma-chaud, to publish in 1659 “Relation de la Mission des Pères de la Compagnie de Jésus Établie Dans le Royaume de Perse par le P. Alexandre de Rhodes.” This was Rhodes’s last missionary contribution. He died in Esfahan on 5 November 1660, some months before the arrival there of Monsignor Lambert de la Motte, the first Vicar Apostolic, who had left Paris for Vietnam and traveled overland on the recommendations of Rome, so as to avoid being spotted by the Portuguese.

The quận ngu alphabet: Alexander of Rhodes’s enduring legacy to Vietnam

Rhodes had taken advantage of his stays in Rome and Paris to publish some of his numerous works, the most important of which are the catechism in Latin and Vietnamese, a small Vietnamese grammar written according to the methods of Latin grammars in French, and the famous Vietnamese-Portuguese-Latin dictionary, the first of the Annamite language written in quận ngu and transcribing Vietnamese phonemes on the basis of Portuguese phonetics. At the time this was a veritable revolution because this writing replaced both chữ nôm, a system of radical-phonetic characters formed from the Chinese characters used between the 12th and 20th centuries AD, and chữ hán, that is, classical Chinese, the language of the administration during the Chinese domination (from 111 BC to 939 AD) and again when reintroduced by the Nguyên dynasty (1804-1954). This romanization was then adopted not only by the French colonial power, which imposed it in 1918 as the official orthography in the school system for Vietnamese children, but also by nationalists, who saw it as a means of uniting local populations who spoke different languages. Simpler to learn than the two other scripts based on Sino-Vietnamese characters, Alexander of Rhodes’ quận ngu romanization was to become a tool in the democratization of education which, in spite of its Western and Catholic origin, was adopted in 1954 as the official Vietnamese administrative writing system, replacing Chinese, which had been kept as the language of the imperial administration by the French colonial power.

Vietnamese history has forgotten the precursors of this vast linguistic mutation—Francisco de Pina, Alexander of Rhodes’s first teacher of Vietnamese, Gaspar do Amaral, and António
Chinese script was introduced in Vietnam as the first written language in 111 BC. As in Japanese, Chinese words account for a huge proportion of the modern Vietnamese vocabulary, even though original pronunciations were altered according to local phonetic patterns. The characters were identical to classical Chinese characters (called Confucian script, chữ nho 子儒, or Chinese script, chữ hán 漢), but eventually, in the 13th century, orthodox Chinese characters were supplemented with new characters specific to Vietnam (chữ nôm 喃, literally, characters for talking). These characters, though modeled on the same structural principles as in China, tended to be very complex and were not understood in China. These two sets of characters taken together are designated by the term chữ nôm 漢喃, or Vietnamese characters. This script, intended as a language learning aid, was perfected and popularized by Alexander of Rhodes, who published the earliest extant Vietnamese-Portuguese-Latin dictionary using quốc ngữ (Dictionary Annamiticum Lusitanum et Latinum). Quốc ngữ remained in little use until the 19th century when the French colonial government hoped it would reduce the pervasive influence of Chinese culture and be a stepping stone toward learning French. Vietnamese reformers in the 20th century saw quốc ngữ as a means to foster mass literacy. The traditional writing system was abolished in 1918, and by 1930 the alphabetic script had become prevalent. Its role as national writing script was never questioned throughout the troubled period of the Vietnam War, by either side. Quốc ngữ, which was officially adopted in 1954, is a very precise phonemic transcription of the spoken language, which accounts for its high understandability—once the system is mastered!

Today there is a revival of cultural interest in the use of the classical characters, epitomized by the Nôm Preservation Foundation, founded in 1999, in the realization that out of 80 million Vietnamese, only fewer than 100 scholars were able to read the ancient “Chinese-like script that Vietnamese used to record their own language and its vast heritage of poetry, history, medicine, and religion, an entire culture about to go extinct.”
Barbosa—the authors of a first Portuguese-Vietnamese dictionary from which Rhodes drew inspiration. But the Jesuit from Avignon has acquired in his country of adoption a cultural aura recognized universally, even by the Communists, as shown in 1990 by a declaration by Cu Huy Can, a minister of culture under President Ho Chi Minh:

"It is to the Reverend Father Alexander of Rhodes that we owe the transcription of Vietnamese in Roman characters, which we call quốc ngu, or national language. That is why this Jesuit, who long ago came from imperialist Europe, is considered in our country as one of the architects of our culture."

Thus it was that three hundred and thirty years after his death, Alexander of Rhodes, neglected by his own people, received the recognition that was his due from the country where he left his heart.

ALEXANDRE DE RHODES : ÉVANGÉLISATEUR HYPERPOLYGLOTTET PÈRE DE L’ALPHABET MODERNE VIETNAMIEN

En 1954, après la signature des accords de Genève qui mettaient fin à la guerre d’Indochine et à presque un siècle de domination française sur l’ancien empire du Dai-Viêt, la nouvelle administration vietnamienne abandonna définitivement l’usage des caractères chinois pour adopter le quốc-ngu. Cette transcription en alphabet latin de la langue locale avait été mise au point, trois siècles auparavant, par un petit groupe de jésuites envoyés par le Padroado portugais parmi lesquels un seul, aujourd’hui, a acquis une stature de personnage majeur dans l’histoire du Vietnam : Alexandre de Rhodes. Il est difficile de trouver missionnaire plus cosmopolite que ce descendant d’une famille de marranes aragonais réfugiée depuis le XVe siècle en Avignon, alors terre pontificale. D’ascendance italienne par sa mère, Français et Provençal par la langue et la culture, il était cependant sujet du pape pour l’état-civil. Étudiant à Rome pendant une dizaine d’années, il séjourna successivement en Inde, en Chine, en Cochinchine et au Tonkin avant de revenir à Rome puis à Paris pour finalement aller mourir en Perse. Cette vie itinérante, jointe à d’exceptionnelles capacités linguistiques, fit de lui un véritable dictionnaire vivant, pratiquant une douzaine de langues, du latin à l’hindoustani et de l’hébreu au chinois, en passant par le grec, le portugais, le provençal, le canarien, le japonais, le vietnamien, l’italien, etc… Cependant, s’il est surtout connu par ses travaux linguistiques en vietnamien, il n’en reste pas moins vrai qu’Alexandre de Rhodes fut aussi un grand missionnaire qui joua un rôle prépondérant dans les débuts de l’évangélisation du Vietnam, puis dans la réforme entreprise par le Vatican au XVIIe siècle afin de libérer les jeunes chrétiénités asiatiques de l’emprise coloniale du Portugal.