Towards achieving remission in the treatment of depression

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The burden of depressive illness constitutes a major public health issue. Despite real progress and better tolerance of new antidepressant medications, a significant number of depressed patients still suffer from rather severe residual depressive symptoms.This relative lack of efficacy clearly interferes with their psychosocial functioning and their quality of life. In addition, it is now well-recognized that the failure to reach full clinical remission after antidepressant treatment involves a high risk of relapse or recurrence in patients suffering from major depression. This paper reviews the concept of remission across different definitions, and the potential risk factors associated with the failure to reach clinical remission. The identification of specific residual symptoms in nonremitted patients is also of great importance, in order to assess the predictive value of those symptoms in relation to relapse and recurrence. Some methodological issues are also discussed, as well as various therapeutic strategies aimed at relieving residual depressive symptoms. Clinical remission remains a gold standard and a primary objective of modern antidepressant therapy.

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Depressive disorders constitute a major public health issue, and are estimated to rank in second position among all diseases by the year 2010, thus contributing heavily to the global burden of diseases in man, according to Murray and Lopez, who conducted a study for the World Health Organization (WHO).[1] Therefore, the effort to alleviate depressive symptoms in the general population is a major public health issue. The concept of clinical remission in the treatment of major depressive disorders has gained growing attention in the last few years. The reasons for this relatively recent interest are manifold. Depressed patients, as well as patient organizations, are not totally satisfied with the current effectiveness and tolerance of available antidepressant medications. Despite the obvious benefits of antidepressants, many depressed patients are still suffering from incapacitating residual symptoms. Furthermore, follow-up investigations have demonstrated that depressed patients who do not reach full remission after antidepressant therapy, that is, patients who are still presenting a number of residual symptoms, are at a higher risk of relapse or recurrence than patients achieving full remission after treatment.[2-4] Conversely, depressed patients who reach full remission after treatment have a better level of functioning[5] and have an improved prognosis[6] compared with patients who are nonremitters.

Adequate clinical remission is therefore of great functional importance for the patient, because it seems to be

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Selected abbreviations and acronyms

HAM - D17	*Hamilton Rating Scale for Depression – 17 items*
HAMD-D7	*Toronto Hamilton Rating Scale for Depression – 7 items*
MADRS	*Montgomery Åsberg Depression Rating Scale*
MIDAS	*Rhode Island Method to Improve Assessments and Services*

a predictor of long-term stability and a rather good indicator of better psychosocial functioning, which is of utmost importance for assessing quality of life in our depressed patients.[7-9] For the above reasons, it becomes of great interest to the scientific community and to our patients to report, in future clinical trials, not only rates of responders but also remission rates, in order to assess the real clinical efficacy of antidepressants and to position new treatments in outcome studies.

Definitions of remission may vary across the literature, and questions arise about the boundaries between full remission and partial remission, the presence after treatment of residual symptoms, and the return or not to premorbid psychosocial functioning. During a consensus conference supported by the MacArthur Foundation, Frank and colleagues[10] came up with a number of operational definitions to assess the complex course of depressive disorders. Partial remission is defined as a period of time with some improvement of symptoms, but not of enough magnitude as to achieve full remission, and with the persistence of some residual symptoms. This state corresponds to a score of 8 to 15 on the Hamilton Rating Scale for Depression (HAM-D17). Conversely, full remission is obtained where clinical improvement is such that the patient becomes almost asymptomatic. Clinical remission is usually defined by a score of 7 or less on the HAM-D17 or a score of 10-12 or less on the Montgomery Åsberg Depression Rating Scale (MADRS).

Zimmerman and Colleagues[11] have analyzed the implications of using various cutoff scores on symptom severity scales in order to define clinical remission in depressed patients as part of the Rhode Island Method to Improve Diagnostic Assessments and Services (MIDAS) project. They also assessed the association between remission status and psychosocial impairments for different cutoff scores for remission in 303 depressed outpatients using the MADRS, the HAM-D17, and an index of the DSM-IV remission status. For both severity scales, the different levels of cutoff scores were associated with different rates of remission. The high cutoff scores were also associated with higher rates of psychosocial impairment.

These results may suggest that the lower the cutoff scores used to define remission, the more valid the results may be in term of clinical relevance and quality of life assessment after antidepressant therapy.

A valuable approach of interest to practising psychiatrists has been proposed by McIntyre and Colleagues,[12] who have designed a shorter version of the HAM-D17 using 7 items out of the 17 items of the original scale, based on frequency and sensitivity to changes after antidepressant treatment. The authors then attempted to validate this shortened questionnaire, called the Toronto HAM-D7, in a sample of 292 patients with major depression followed up in a depression clinic in Toronto.

The results indicate that a score of three or less on the Toronto HAM-D7 did correlate with the score of seven or less for remission on the 17 items of the HAM-D17. If this is confirmed in additional validation studies, the Toronto HAM-D7 Scale could be of practical use for general practitioners and for psychiatrists, as well as for use as a screening tool to be used in some antidepressant trials. An American College of Neuropsychopharmacology (ACNP) Task Force reached consensus guidelines after conducting a critical review of the literature and exchanging expert clinical experience. The ACNP Task Force then made several recommendations, which are, however, generally not evidence-based, on the concept of remission in major depressive disorders.[6] *Table I* summarizes some of the ACNP Task Force recommendations.

The ACNP Task Force also reviewed the literature on potential associated factors which may influence the remission, the time of remission and the stability of the remission.[6] These factors include among others the type of treatment, the dose, the duration of treatment, baseline severity of depressive symptoms, the stage of treatment resistance (TRD), the compliance, the presence of DSM-IV Axis I, II, or III conditions, environmental stressors, the degree of social support, and the retrospective morbidity of the illness, as well as neurobiological and genetic vulnerability.

There is no general consensus about the length of time the depressed patient in remission should remain in remission, but, according to most experts, this period of remission is expected to last between 4 and 6 months to be of clinical relevance for the patient.[10]

The length of the remission period is obviously of great clinical relevance to the patient, and is also contingent on the continuation of antidepressant treatment. In a review of 31 randomized trials, Geddes and Colleagues[13] have shown that continuing treatment with antidepressants reduced the risk of relapse by 70% compared with treatment discontinuation. The treatment effect seemed to persist for between 12 and 36 months.

A long-term naturalistic study conducted in Japan by Furukawa and Colleagues in a cohort of 95 unipolar major depressive patients followed up for a 10-year period was recently reported.[14] The authors assessed the definition of recovery according to the length of time of remission. Based on the results, they concluded that a period of 2 months of remission was too short to define recovery, but proposed that a period of 4 to 6 months of remission may be more adequate. This study, however, was not controlled and the sample size was too small to draw definitive conclusions.

Unfortunately, as previously stated, a significant number of patients do not remain symptom-free and continue to present subsyndromal depression or subthreshold depression for some time during their lifetime. These patients have been shown to have a higher risk of early relapse into depression, lower levels of social and psychological functioning, and greater rates of physical morbidity such as cardiovascular disease and stroke, as well as higher rates of mortality.[15] Thase has reported that more than one third of depressed patients will reach remission after acute antidepressant treatment.[16] Most clinical trials report remission rates of 22% to 40%,[17] while effectiveness studies including representative samples of depressed patients closer to clinical practice report lower remission rates—around 11% to 30%.[18-21] The identification of predicting factors of nonremission (the persistence of residual symptoms) in antidepressant therapy has not been conclusive for such factors as personality traits, the impact of life events, and even baseline severity level of depression.[15] Some authors, such as Zimmerman et al,[22] have proposed that the concept of remission not be restricted to scores of symptoms on severity scales like the HAM-17 or MADRS, but that the definition of remission be enlarged to the restoration of normal functioning and the improvement of quality of life. This conclusion was reached based on the results of the MIDAS project, in which 514 depressed patients were asked for their subjective evaluation of their remission status in relation to the severity levels of their depressive illness and their degree of functional impairment.

These variables were found to be correlated and also predictive of their remission state. McGlinchey and Colleagues[23] have evaluated factors such as gender, age, and depressed state on patient's perspectives of remission. They were able to complete a survey in 560 depressed outpatients using The Standardized Clinical Outcome Rating Scale for Depression (SCOR-D) an instrument including DSM-IV criteria for major depressive episodes and for psychosocial impairment. The results showed that the perspective on remission was different in men compared with women, as well as in older versus younger depressed patients. Female depressed patients related the perception of remission more to emotional stability, and older depressed patients emphasized more the necessity to reach a state of well-being.

Several therapeutic strategies have been proposed to achieve remission[16] or to treat residual symptoms in patients suffering major depressive disorders.[24] Among the most frequent residual symptoms targeted, one finds anxiety symptoms, sleep disturbances, depressed mood, work difficulties, fatigue, and lack of interest.[15,24,25]

The rather high rate of manifestation of residual symptoms observed in nonremitted depressed patients justifies the need for research into various therapeutic strategies such as switching, augmentation, combination therapies,

Remission
• A primary end point in acute antidepressant treatment
• Is present if equal or more than 3 weeks
• Day-to-day function is secondary outcome
• Trials using remission as primary outcome must last longer (12-20 weeks)
Relapse
• Occurs following remission and before recovery
• Requires a DSM-IV diagnostic criteria for Major Depressive Episode (MDE) to be met
Recovery
• Can only be defined after more than 4 months following the onset of remission
Recurrence
• Occurrence of MDE defined by DSM-IV
• Occurs after the onset of recovery

Table I. Summary of ACNP Task Force recommendations.
Adapted from ref 6: Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on Response and Remission in Major Depressive Disorder. *Neuropsychopharmacology*. 2006;31:1841-1853. Copyright © Nature Publishing Group 2006

including with cognitive behavioral therapy, and the search for new targets to develop novel and more efficacious antidepressant treatments. This strategy has been applied in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study[26] which has a rather complex and problematic design and which examines, among several issues, the rates of remission and time to remission after an initial treatment with a selective serotonin reuptake inhibitor, in this case citalopram, and after subsequent treatment steps, including switching to bupropion sustained-release, cognitive behavioral therapy, sertraline, venlafaxine extended-release, or augmentation of citalopram with bupropion sustained-release, buspirone, or cognitive therapy.

Remission rate after the first step was about 30%, and jumped to 50% after the second phase of treatment, but did not improve after subsequent treatments. An important observation from the STAR*D Study was that a large number of patients in each treatment group did not actually reach remission after 6 to 8 weeks of treatment. Thus, the remission state may indeed take more time to achieve in comparison with a simple response in antidepressant trials. Thus, future trials designed to assess remission as the primary end point in acute treatment studies should probably last at least 8 weeks, and maybe more.

Conclusion

There is general consensus to consider remission after acute antidepressant treatment as the gold standard and main objective of modern antidepressant therapy, but, before the dream becomes reality for the great majority of our depressed patients, innovative strategies and novel etiology-based therapeutic approaches will have to be explored in rigorous controlled investigations combining creative clinical expertise and innovative biomarker research. ❑

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La obtención de la remisión como objetivo de la terapia de la depresión

La carga de la enfermedad depresiva constituye un tema muy importante de salud pública. A pesar del progreso real y de la mejor tolerabilidad de los nuevos medicamentos antidepresivos, un número significativo de pacientes con depresión todavía sufre de bastantes síntomas depresivos residuales graves. Esta relativa falta de eficacia claramente interfiere con su funcionamiento psicosocial y su calidad de vida. Además, actualmente está bien reconocido que el fracaso en la obtención de la remisión clínica completa después del tratamiento antidepresivo involucra un alto riesgo de recaídas o recurrencias en pacientes que padecen de depresión mayor. Este artículo revisa el concepto de remisión a través de diferentes definiciones, y los potenciales factores de riesgo asociados con el fracaso en la obtención de la remisión clínica. También es de gran importancia la identificación de síntomas residuales específicos en pacientes que no remiten, para evaluar el valor predictor de dichos síntomas en relación con recaídas y recurrencias. Asimismo se discuten algunos temas metodológicos, al igual que varias estrategias terapéuticas orientadas al alivio de los síntomas depresivos residuales. La remisión clínica persiste como el gold standard *y es un objetivo primordial de la moderna terapia antidepresiva.*

Vers la rémission dans le traitement de la dépression

Le fardeau de la maladie dépressive est un problème majeur de santé publique. Malgré les progrès réels et la meilleure tolérance des nouveaux antidépresseurs, un nombre significatif de patients déprimés se plaignent encore de symptômes dépressifs résiduels sévères. Ce manque relatif d'efficacité interfère nettement avec leur fonctionnement psychosocial et leur qualité de vie. Le risque élevé de rechute ou de récidive après un traitement antidépresseur n'ayant pas permis une rémission clinique complète chez des patients souffrant de dépression majeure, est maintenant bien reconnu. Cet article analyse le concept de rémission à travers différentes définitions ainsi que les facteurs potentiels de risque associés à son échec. Identifier les symptômes résiduels spécifiques chez des patients sans rémission est aussi très important afin d'évaluer leur valeur prédictive dans la rechute et la récidive. Certaines questions méthodologiques sont traitées, comme les différentes stratégies thérapeutiques visant à soulager les symptômes dépressifs résiduels. La rémission clinique est un critère de référence et le premier objectif d'un traitement antidépresseur moderne.