REMISSION IN DEPRESSION AFTER TREATMENT: TOO OBVIOUS TO CLINICIANS, WHY SO DIFFICULT TO MEASURE?

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Abstract
The standard of reference for the prognosis of depression has substantially changed from "response" to "remission", since this last is associated with better indices of the course of illness. The treating psychiatrist must now reconsider his approach and refer to remission as the ultimate goal of treatment. Otherwise, patients with incomplete remission could even blame the treating psychiatrist for their enduring illness. The use of simple, short psychometric scales, like the CGI-S, could facilitate this approach, since scores of "1" and "2" are reasonable proxy for remission, as shown by recent literature.

Key words: Depression, remission, Hamilton Depression Scale, Clinical Global Impression

The border between a successful treatment and a failed treatment in medicine is based on whether pre-established goals are reached. These standards are accepted by the international scientific community and are susceptible to variation over time as knowledge progresses.
In general, when evaluating the effectiveness of a given treatment, medical doctors rely on objective and quantitative measures, such as blood pressure, electrocardiograms, blood chemistry and imaging techniques; these measures are directly related to the pathophysiology of a given disorder.
Psychiatry is most probably a major exception to this approach, because in this discipline the outcome evaluation is still based on purely descriptive information, taken from a direct visit with the patient. This evaluation has a broad range of subjective interpretations and is in no way connected to the pathophysiology of the disorder.
In this general framework, different labels have been used to evaluate the efficacy of antidepressant treatments after the introduction of tricyclics and the mono-ammine oxidase inhibitors: "improvement", "response", "clinical remission" or, more rarely "functional remission" and "recovery".
Some of these indicators, for example, "functional remission" and "recovery", are more a wishful goal than really true measures to evaluate a successful treatment. To satisfy these definitions, other factors are needed that are independent from drug treatment. The factors that could favour or hamper a full "functional remission" and/or "recovery" should definitely include the attitude of persons in close contact with the patient toward depression, difficulties in starting a new job under actual economic conditions, and, more generally speaking, the presence of barriers due to the stigma related to mental illness in general and its treatment.

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From a broader perspective, one must realize that the different criteria to evaluate a successful antidepressant treatment have substantially different meanings. For example, “improvement” and “response” imply a reference to a previous evaluation, whereas “clinical remission”, “functional remission” and “recovery” are in some ways an almost absolute state, unrelated to any previous phase of a patient’s history. Furthermore, “response”, “clinical remission”, “functional remission” and “recovery” refer to definite cut-offs on psychometric scales, whereas “improvement” does not imply pre-defined quantitative criteria, for it simply describes the pure judgement that the clinical picture is somehow better compared with a previous evaluation and does not commit to any estimate of the rate of improvement. Finally, “improvement”, “clinical remission”, “functional remission” and “recovery” also still maintain their value and meaning when no specific treatment is started, whereas the label “response” should more properly satisfy the assumption of a definite cause–effect link between treatment and amelioration of the clinical condition.

All these differences are not purely semantic. On the contrary, they have a substantial effect on the prognosis of a patient with depression. It is notable that the indicators of a successful treatment have changed from “improvement” and “response” to the more recent and more rigorous “clinical remission”.

Compared with patients showing improvement or a general response to treatment, those who reach “clinical remission” have many better prognostic indicators. A huge amount of data from the recent literature clearly state that, compared with those who are responders only, patients with “clinical remission” have a lower number of relapses and recurrences, have a longer euthymic period, a lower risk of a chronic course, as well as a better working and social functioning, less days off work, a less frequent unemployment status, and a lower use of general medical services [1-14].

These data strongly sustain the unanimous position of the scientific community that has established “clinical remission” as the gold standard for a successful treatment, which means reaching an almost or even completely asymptomatic state. However, this largely held conviction is not echoed by a unique choice of criteria and evaluation scales to designate the state of “clinical remission”. Indeed, time after time, different rating scales have been used, particularly the Hamilton Rating Scale for Depression, the Montgomery-Äsberg Depression Rating Scale and the Quick Inventory for Depressive Symptomatology, and even different versions of the same scale, different cut-off scores, and different time lengths for “clinical remission” [8,11,13]. Not surprisingly, these differences are sometimes associated with differences in results [13].

Despite this variability in criteria, the standard of “clinical remission” has been widely accepted in clinical studies on the effectiveness of different antidepressant treatments, both pharmacologic and nonpharmacologic. This is proved by the fact that, since the new millennium, almost all trials on the treatment of depression published in international journals have included a state of “clinical remission” among the different indicators of a successful treatment.

In the routine clinical treatment of depression, acceptance of the concept of “clinical remission” as a necessary reference to define a successful treatment is far less rooted. Some doctors, psychiatrists or not, aim to reach a “clinical remission” state in their treatment efforts, but many others, the majority throughout the world, still pursue a vague “improvement” or a good “response” as the ultimate treatment goal for their patients. The choice of not updating one’s decisional algorithm about depression treatment according to proper assessment standards means that a treatment project cannot be correctly implemented; if a clinician is satisfied with the “improvement” or “response” of his patient without having reached “clinical remission”, he or she will be supporting the continuation of drugs that are only partially effective, and avoiding a change in drug posology or treatment until “clinical remission” is reached. For the patient, this means possibly damaging care over time, not deserved, that could lead to a legal case for malpractice. For these reasons, it is mandatory that the doctor treats a patient with depression with the settled goal of “clinical remission”.

The need to identify a definite anchor point to state if a patient with depression is in “clinical remission” is generally accepted in the research field, but in clinical practice it cannot be transferred easily, because the use of psychometric scales and structured interviews is still largely an exception. The reasons why clinicians are not used to considering psychometric tools as the basis for a proper evaluation are manifold.

Among these are the lack of training in using rating scales, not being acquainted with the basic principles of the reliability and validity of a scale, considering the products of scientific reports as academic affairs that are not to be fully and quickly transferred to clinical practice, the inadequacy of training networks, and, most of all, the work burden that is supposedly

limiting the time available to properly administer the rating scales.

The lack of available time may be only a partial justification. Indeed, it is true that 15-20 minutes are needed to complete the Hamilton Rating Scale for Depression and the Montgomery-Äsberg Depression Scale, but it is also true that the Quick Inventory of Depressive Symptomatology needs only 5-10 minutes and this does not truly vary the length of time required for the clinical evaluation of a depressed patient.

Furthermore, the Quick Inventory of Depressive Symptomatology is often used effectively in its self-administered form, so that it does not interfere with the timetable of the physician. Psychiatrists who are very refractory to the use of rating scales to diagnose clinical remission of depression should use at least the Clinical Global Impression-Severity Scale. There are two main reasons for recommending it. First, this scale bypasses the issue of time available on the part of the clinician because it quickly rates the severity of depression, as this unravels during the routine clinical evaluation. To rate the scale requires only 1-2 minutes. Second, since the Clinical Global Impression scores correlate well with the Hamilton Rating Scale for Depression and the Montgomery-Äsberg Depression Scale [15], one can assume that a score of "1" and possibly "2" stands for "clinical remission".

Actually, in a recently published study [13] on remission in 907 outpatients treated with antidepressant medications by 41 community psychiatric centres in Italy, the VIVAL-D study, we found that the correlation between Clinical Global Impression-Severity Scale scores and the HAM-D17 was very high, with a Spearman correlation coefficient of 0.63, and, taking the usual HAM-D17 cut-off of 7/8, patients with a CGI rating of "1" and "2" were in clinical remission in 92.3% and 57.3% of cases, respectively. Our results further underline how clinicians can make a reliable and valid rating of remission through the use of quick and easy psychometric scales.

We also found that only a minority of patients reached a complete symptom-free condition. This in turn should alert clinicians to the possibility that a few symptoms may hinder functional remission. It is reported [16] that cognitive disturbances are among the most common residual symptoms of depression in spite of treatment, and probably newer pharmacological approaches to cognitive dysfunction will be needed that will cooperate with other interventions.

Recent findings have revealed that antidepressant drugs reactivate a window of plasticity in the adult cortex [17] and that functional remission from depression is a gradual process that unfolds slowly, facilitated by structured guidance and rehabilitation. The evaluation of psychosocial functioning and health related quality of life has been poorly investigated by recent research [18], but the CGI, while asking a clinician to compare a subject to typical patients in the clinical experience, encompasses some evaluation of the overall performance too.

Finally, although every effort should be pursued by the psychiatrist in treating aggressively depression, a clinician must remember that some variables may hinder remission, like temperament [18] and epigenetic effects during early development [17].

However, if the knowledge about remission would inform the clinical approach to a depressed patient, the quality of treatment will ultimately improve, with significant impact on a patient wellbeing and overall performance.

Take home messages for psychiatric care

- The standard of reference for the prognosis of depression has now changed from "response" to "remission"
- Data from the literature evidence many better prognostic indicators associated with remission
- Improvement or response should no longer be the ultimate goal of treatment
- Not treating a patient until remission could possibly lead to a legal case for malpractice
- The use of psychometric scales in clinical practice is still largely an exception
- The Clinical Global Impression – Severity Scale requires only 1-2 minutes to be rated
- Data from a recent, large epidemiological survey in 41 psychiatric centers of Italy have shown that ratings of "1" and "2" of the CGI were valid proxy for clinical remission

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