Differences Between Minimally Depressed Patients Who Do and Do Not Consider Themselves to Be in Remission

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Objective: We recently derived a cutoff on a self-report scale corresponding to the most commonly used definition of remission in depression treatment studies (i.e., Hamilton Rating Scale for Depression [HAM-D] score ≤ 7). However, recent research has suggested that use of this cutoff on the HAM-D to define remission is overinclusive. The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to examine how many depressed patients in ongoing treatment who are considered to be in remission by a self-report equivalent of the HAM-D definition of remission nonetheless do not consider themselves to be in remission.

Method: Five hundred thirty-five psychiatric outpatients treated for a DSM-IV major depressive episode were asked whether they considered themselves to be in remission and completed the Clinically Useful Depression Outcome Scale (CUDOS), a measure of the severity of the DSM-IV symptoms of depression. The study was conducted from August 2003 until July 2004.

Results: Nearly one quarter of the patients who met the remission threshold on the CUDOS (55/249) did not consider themselves to be in remission. Among the CUDOS remitters, the total score on the CUDOS was significantly lower ($p < .001$) in patients who considered themselves to be in remission than in patients who did not indicate that they were in remission. Examination of specific symptoms revealed greater appetite disturbance and hypersomnia in the patients who did not think they were in remission.

Conclusions: Our results suggest that heterogeneity of clinical status exists even among patients who are minimally depressed and considered to be in remission according to contemporary definitions on symptom severity scales.

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In describing treatment outcome in antidepressant efficacy trials, it is common to define treatment response as an improvement of 50% or more in scores on symptom measures such as the Hamilton Rating Scale for Depression (HAM-D)[1] and remission as a score below a predetermined cutoff score on the scale. Recognizing remission among patients who have responded to treatment is clinically important because the presence of residual symptoms in treatment responders predicts an increased likelihood of relapse.[2–5] Because of the prognostic significance of residual symptoms, experts in the treatment of depression have suggested that achieving remission should be viewed as the primary goal.[6–12]

Through the years, many cutoff scores have been used on the HAM-D to define remission[13,14]; however, since the publication of the recommendations of Frank and colleagues,[15] a general consensus has emerged to define remission on the HAM-D as a score of 7 or less. Research from our laboratory, however, has questioned the validity of this cutoff and suggested that a lower cutoff score is a more valid indicator of remission.[16] Our results were consistent with the findings of Judd and colleagues,[17] who found that patients who had "recovered" but had a low level of residual symptoms were at greater risk of relapse compared with recovered patients who were completely asymptomatic. Extrapolating from their findings, Judd et al. suggested that the cutoff score of 7 on the HAM-D to identify remission was too high. Thus, there is some uncertainty as to how asymptomatic patients should be in order to consider them to be in remission.

Recently, we demonstrated that a self-report scale could be used to identify remission in depressed outpa-

tients.[18] Specifically, we found that a cutoff on a self-report depression scale could be derived that corresponded highly to the commonly used definition of remission on the HAM-D (i.e., score ≤ 7).

The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to examine how many depressed patients in ongoing treatment who are considered to be in remission by a self-report equivalent of the Frank et al.[15] definition of remission on the HAM-D nonetheless do not consider themselves to be in remission. If recent research is correct in indicating that use of the cutoff of ≤ 7 on the HAM-D to define remission is overinclusive, then we would expect that a substantial number of these patients would not consider themselves to be in remission. We then compared the symptom profiles of patients who did and did not consider themselves to be in remission.

METHOD

The study was conducted from August 2003 until July 2004. Participants were 535 psychiatric outpatients who were being treated for a DSM-IV major depressive episode in the Rhode Island Hospital Department of Psychiatry outpatient practice. This private practice group predominantly treats individuals with medical insurance on a fee-for-service basis, and it is distinct from the hospital's outpatient residency training clinic that predominantly serves lower income, uninsured, and medical assistance patients. For some patients, the diagnosis of major depressive disorder (MDD) was based on the Structured Clinical Interview for DSM-IV (SCID),[19] whereas others were diagnosed on the basis of an unstructured clinical interview. We did not record how many patients were interviewed with the SCID. The sample included 182 men (34.0%) and 353 women (66.0%) who ranged in age from 21 to 80 years (mean = 44.2 years, SD = 11.5). The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed, written consent.

Patients completed 2 questionnaires. During the past several years, as part of the MIDAS project, we have developed several disorder-specific interview-based and self-report screening and outcome measures that were designed to be easily incorporated into routine clinical practice.[20] One such measure is the Clinically Useful Depression Outcome Scale (CUDOS). The CUDOS contains 18 items assessing each of the DSM-IV inclusion criteria for MDD and dysthymic disorder as well as psychosocial impairment and quality of life. Compound DSM-IV symptom criteria referring to more than 1 construct (e.g., problems concentrating or making decisions, insomnia or hypersomnia) were subdivided into their respective components, and a CUDOS item was written for each component. The respondent is instructed to rate the symptom items on a 5-point Likert scale indicating "how well the item describes you during the past week, including today" (0 = not at all true/0 days, 1 = rarely true/1–2 days, 2 = sometimes true/3–4 days, 3 = often true/5–6 days, 4 = almost always true/every day). A Likert rating of the symptom statements was preferred in order to keep the scale brief. The scale is available from the lead author (M.Z.) upon request.

The initial studies of the reliability and validity of the CUDOS have indicated that the scale has strong psychometric properties (M.Z.; T. Sheeran, Ph.D.; I. Chelminski, Ph.D., manuscript in preparation). Five hundred sixty-eight psychiatric outpatients completed the scale, and the internal consistency reliability coefficient was 0.90. Test-retest reliability, examined in 176 patients who completed the scale a second time within a week of the first administration, was 0.92. The CUDOS was significantly correlated with the HAM-D (r = 0.69) and the Clinical Global Impressions-Severity of Illness scale[21] (r = 0.71), clinician ratings of the severity of depressive symptoms, as well as with the self-rated Beck Depression Inventory[22] (r = 0.81). Thus, the CUDOS is a psychometrically strong instrument that correlates highly with clinician ratings of depression yet is brief enough to be easily incorporated into clinical practice because on average it takes less than 2 minutes to complete.

In a second validation study of the CUDOS, the scale was completed by 267 depressed outpatients in ongoing treatment who were also rated on the 17-item HAM-D.[18] The mean score on the 17-item HAM-D for the 267 depressed outpatients was 11.1 (SD = 8.4; range, 0–36). The Pearson correlation between the HAM-D and the CUDOS was 0.89. We examined the ability of the CUDOS to identify patients who were in remission according to the HAM-D across the range of CUDOS cutoff scores by conducting a receiver operating curve analysis. The sensitivity, specificity, and overall classification rate of the CUDOS for identifying remission according to the HAM-D threshold score of ≤ 7 were examined for each CUDOS total score. On the basis of a cutoff score < 20, the CUDOS had a high level of agreement with the HAM-D definition of remission (sensitivity = 87.4%, specificity = 87.8%, total agreement = 87.6%, kappa = 0.75).

The second questionnaire used in the present study assessed patients' opinions regarding the importance of different factors in determining remission from depression. On the front of the 2-sided questionnaire, the instructions read as follows:

> During the past decade, researchers who study the treatment of depression have discussed the best method of evaluating response to treatment. One area of controversy is what are the most important factors in determining who has responded well to treatment. Some experts say that the most important thing to look at are the symptoms of depression—a

person should be considered in remission when the symptoms of depression (such as depressed mood, sleep and appetite changes, fatigue, problems concentrating, etc.) have gone away. Other experts say that the most important thing to look at is how a person is functioning, regardless of whether they are still experiencing some symptoms of depression. Other aspects of remission have also been proposed.

The purpose of this brief questionnaire is to learn what patients believe are the most important factors in determining whether someone is in remission from their depression. Please rate how important you think each of the following factors are in determining whether someone is in remission from depression. After rating the importance of each item circle the number of the item that you think is the most important factor.

Before completing the questionnaire, please provide the following background information:

The questions eliciting background information included gender, age, education, and a question regarding the patient's perception of whether he or she was currently in remission from depression (0 = yes, 1 = no).

Data Analysis

In our previous study, we established that a cutoff score of 20 on the CUDOS highly corresponded to the HAM-D definition of remission. Our interest in the present report was to examine whether heterogeneity remained within the group of patients that met this definition of remission. Therefore, we selected patients scoring below 20 on the CUDOS and then subdivided them into 2 groups based on whether or not they considered themselves to be in remission. We used the χ^2 statistic to compare the 2 groups on categorical variables and t tests to compare them on continuous variables. Because no prior study has been conducted on this topic, we considered our analyses exploratory and did not correct for multiple comparisons.

RESULTS

Fifty-four (10.1%) of the 535 patients were excluded because they did not answer all of the questions on the CUDOS, thereby leaving a sample of 481 patients. There were no statistically significant demographic differences between the patients who did and did not complete the scale. Slightly more than half of the sample (53.2%, N = 256) scored below 20 on the CUDOS and were considered to be in remission. Seven (2.7%) of the 256 patients who scored below 20 on the CUDOS did not answer the question regarding remission status, leaving a sample of 249 patients. There were no significant demographic differences between the patients who did and did not answer this question.

Table 1. Demographic Characteristics of Minimally Depressed Outpatients in Psychiatric Treatment Who Did and Did Not Consider Themselves to Be in Remission[a]

Characteristic	Self-Reported Remitted[b] (N = 194)	Self-Reported Not Remitted (N = 55)
Sex, N (%)		
Female	134 (69.1)	37 (67.3)
Male	60 (30.9)	18 (32.7)
Education, N (%)		
Less than high school graduate	5 (2.7)	1 (1.8)
High school graduate	95 (50.5)	33 (60.0)
College graduate	88 (46.8)	21 (38.2)
Age, mean (SD), y	45.4 (11.6)	42.2 (11.9)

[a]None of the differences between groups was statistically significant.
[b]Data on education status missing for 6 patients in the remission group.

One hundred ninety-four (77.9%) of the 249 patients who were in remission according to the CUDOS indicated that they were in remission on the yes-no question directly evaluating self-perceived remission status, and 55 (22.1%) did not consider themselves to be in remission. The data in Table 1 show that there were no differences in age, gender, or education between the patients who did and did not consider themselves to be in remission.

The mean ± SD total score on the CUDOS was significantly lower in patients who considered themselves to be in remission than in patients who did not indicate that they were in remission (8.4 ± 5.4 vs. 12.6 ± 5.0, $t = 5.06$, $p < .001$). The patients who were in remission were significantly less likely to report 1 or more symptoms of depression occurring every day or nearly every day (25.3% vs. 50.9%, $\chi^2 = 13.2$, $p < .001$). Regarding specific symptoms, the data in Table 2 show that the patients who indicated that they were not in remission were significantly more likely to report appetite disturbance and hypersomnia.

DISCUSSION

Our results suggest that heterogeneity of clinical status exists even among patients who are considered to be in remission according to contemporary definitions on symptom severity measures. Nearly one quarter of the patients who met the remission threshold on the CUDOS nevertheless did not consider themselves to be in remission. Among the CUDOS remitters, a comparison of self-rated remitters and nonremitters yielded expected differences in symptom severity. Examination of specific symptom differences revealed greater appetite disturbance and hypersomnia in the patients who did not think they were in remission.

What might be the clinical significance of these findings? We would expect that patients who do not consider themselves to be in remission are more likely to want changes in their treatment. Interestingly, the minimally

Table 2. Depressive Symptoms in Minimally Depressed Outpatients Who Did and Did Not Consider Themselves to Be in Remission

	Self-Reported Remitted (N = 194)		Self-Reported Not Remitted (N = 55)	
Depressive Symptom	N	%	N	%
Sad or depressed	3	1.5	1	1.8
Anhedonia	2	1.0	0	0.0
Poor appetite	2[a]	1.0	3	5.5
Greater appetite	7[b]	3.6	9	16.4
Difficulty sleeping	14	7.2	5	9.1
Sleeping too much	3[a]	1.5	4	7.3
Psychomotor agitation	7	3.6	1	1.8
Psychomotor retardation	4	2.1	4	7.3
Fatigue	10	5.2	5	9.1
Guilt	4	2.1	4	7.3
Worthlessness	1	0.5	1	1.8
Problems concentrating	9	4.6	2	3.6
Indecisiveness	0	0.0	0	0.0
Wished I were dead	0	0.0	0	0.0
Suicidal thoughts	0	0.0	0	0.0
Hopelessness	1	0.5	0	0.0

[a]Significant at $p < .05$.
[b]Significant at $p < .01$.

depressed outpatients who did and did not indicate that they were in remission differed in somatic symptoms of depression but not cognitive symptoms. We cannot rule out the possibility that the reports of sleep and appetite disturbance represent, in part, medication side effects rather than true symptoms of depression. Regardless of the cause, the presence of these symptoms influences patients' self-assessment of remission status and potentially increases the likelihood of requested changes in treatment.

The CUDOS reflects the DSM-IV criteria for MDD, which have been criticized for being overly represented by psychological in contrast to physical symptoms.[23] Other somatic symptoms such as headaches, backaches, musculoskeletal complaints, or muscle tension might also differentiate between patients who do and do not consider themselves to be in remission.

The findings also have implications for the threshold used on symptom inventories to define remission. The relatively large percentage of patients who met the CUDOS definition of remission but did not consider themselves to be in remission suggests that the CUDOS threshold may be too inclusive. This is consistent with our research suggesting that the cutoff score of ≤ 7 on the HAM-D as used to define remission may be too high. We previously have examined the validity of different cutoff scores on the 17-item HAM-D in a series of articles.[16,24,25] We found heterogeneity among patients who were defined as remitted using the cutoff of ≤ 7 such that patients with higher scores on the HAM-D demonstrated greater psychosocial morbidity than lower-scoring remitters, thereby suggesting that the threshold to define remission should be lowered. We, and others, have also found that some patients scoring ≤ 7 on the HAM-D simultaneously met criteria for a depressive disorder.[25,26] There is a conceptual problem with a definition of remission that allows for individuals who continue to meet criteria for the disorder to also be considered in remission. The results of the present study, while not based on the HAM-D per se but instead on a self-report scale that is highly concordant with the HAM-D definition of remission, are consistent with other findings questioning use of the cutoff score of ≤ 7 on the HAM-D to define remission.

Several limitations of the study should be noted. The study was conducted in a single outpatient practice in which the majority of the patients were white and female and had health insurance. The generalizability to samples with different demographic characteristics needs to be demonstrated.

The patients were recruited after having been in treatment for varying lengths of time. While all patients were receiving pharmacotherapy, only a subset was in ongoing psychotherapy. Unfortunately, this information was not recorded. It is unknown how patients' conceptualization of remission might be influenced by their treatment experience. Patients with comorbid conditions were included, though the influence of comorbid conditions on ratings of symptoms, impairment, and remission is unknown. However, heterogeneity in treatment effort, comorbidity, and other clinical and psychosocial parameters such as the number of prior episodes, episode duration, and intervening life events increase the generalizability of the findings to depressed patients in ongoing outpatient treatment.

The assessment of remission status was based on a single yes-no question on a paper-and-pencil questionnaire. It is possible that some patients did not understand the meaning of the term *remission*, although the term was defined in the instructions of the questionnaire. Nonetheless, patients may have had varying conceptualizations of remission. Psychiatric researchers have different opinions regarding the concept of remission, so it would not be surprising for patients to differ. In fact, this variability is one of the reasons for conducting the study. Because patients' self-perceptions of remission status are likely to be associated with requests for treatment modification, it is important to better understand the symptom differences between patients who do and do not consider themselves to be in remission. Finally, in another report, we found expected differences in symptom severity, psychosocial functioning, and quality of life between patients who did and did not indicate that they were in remission, thereby lending support to the validity of the assessment of remission status.[27]

The assessments of overall symptom severity and specific symptoms were based on a relatively new self-report questionnaire. The CUDOS has been validated as a measure of remission status when compared with the HAM-D

definition of remission, and there is good agreement at the symptom level when compared with clinician assessments of specific symptoms. However, it has not yet received study by other investigators.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
2. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–1180
3. Van London L, Molenaar RP, Goekoop JG, et al. Three- to 5-year prospective follow-up of outcome in major depression. Psychol Med 1998;28:731–735
4. Pintor L, Gasto C, Navarro V, et al. Relapse of major depression after complete and partial remission during a 2-year follow-up. J Affect Disord 2003;73:237–244
5. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry 1992;149:1046–1052
6. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. J Clin Psychiatry 1999;60(suppl 22):29–34
7. Nierenberg AA, Wright EC. Evolution of remission as the new standard in treatment of depression. J Clin Psychiatry 1999;60:7–11
8. Ferrier IN. Treatment of major depression: is improvement enough? J Clin Psychiatry 1999;60(suppl 6):10–14
9. Rush AJ, Crismon ML, Toprac MG, et al. Consensus guidelines in the treatment of major depressive disorder. J Clin Psychiatry 1998;59 (suppl 20):73–84
10. Rush A, Trivedi M. Treating depression to remission. Psychiatr Ann 1995;25:704–709
11. Stahl SM. Why settle for silver, when you can go for gold? response vs recovery as the goal of antidepressant therapy [BRAINSTORMS]. J Clin Psychiatry 1999;60:213–214
12. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. J Clin Psychiatry 2003;64(suppl 13):18–25
13. Zimmerman M, Coryell W, Pfohl B. The treatment validity of DSM-III melancholic subtyping. Psychiatry Res 1985;16:37–43
14. Keller M. Past, present, and future directions for defining optimal treatment outcome in depression. JAMA 2003;289:3152–3160
15. Frank E, Prien R, Jarrett R, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry 1991;48:851–855
16. Zimmerman M, Posternak M, Chelminski I. Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? J Nerv Ment Dis 2005;193:170–175
17. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
18. Zimmerman M, Posternak M, Chelminski I. Using a self-report depression scale to identify remission in depressed outpatients. Am J Psychiatry 2004;161:1911–1913
19. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P, version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
20. Zimmerman M. Integrating the assessment methods of researchers in routine clinical practice: The Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project. In: First M, ed. Standardized Evaluation in Clinical Practice, vol 22. Washington, DC: American Psychiatric Publishing, Inc; 2003:29–74
21. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
22. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
23. Fava M. Somatic symptoms, depression, and antidepressant treatment. J Clin Psychiatry 2002;63:305–307
24. Zimmerman M, Chelminski I, Posternak M. A review of studies of the Hamilton Depression Rating Scale in healthy controls: implications for the definition of remission in treatment studies of depression. J Nerv Ment Dis 2004;192:595–601
25. Zimmerman M, Posternak M, Chelminski I. Implications of using different cutoffs on symptom severity scales to define remission from depression. Int Clin Psychopharmacol 2004;19:215–220
26. Brown PJ, Recupero PR, Stout R. PTSD substance abuse comorbidity and treatment utilization. Addict Behav 1995;20:251–254
27. Zimmerman M, McGlinchey J, Posternak M, et al. Remission in depressed outpatients: more than just symptom resolution? Presented at the 158th Annual Meeting of the American Psychiatric Association; May 2005; Atlanta, Ga

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