Early Response and Remission as Predictors of a Good Outcome of a Major Depressive Episode at 12-Month Follow-Up: A Prospective, Longitudinal, Observational Study

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ABSTRACT

Objective: The goal of treating major depressive disorder (MDD) should be not only achieving remission in a particular episode but also avoiding relapses and attaining long-term recovery. The current study was designed to evaluate whether response and remission achieved within the first 6 weeks of antidepressant treatment are associated with a 12-month good outcome (achieving remission by 6 months and remaining in remission until the end of follow-up).

Method: This prospective, longitudinal, multicenter study included adult outpatients who had a *DSM-IV* diagnosis of MDD, baseline scores ≥ 15 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), Clinical Global Impressions-Severity of Illness scores ≥ 4, and a minimum remission period of 12 weeks between the index episode and the immediately prior episode (or who were in their first MDD episode). The primary efficacy measure was early response (a 50% decrease from baseline in $HDRS_{17}$ score by week 6). The secondary efficacy measure was early remission ($HDRS_{17}$ score ≤ 7 by week 6).

Results: Among the total of 930 patients included from December 2006 to June 2007, 38.2% showed early response, and 20.5% showed early remission. Of the early responders, 76.1% had a 12-month good outcome as compared to 81.1% of early remitters. Logistic regression showed that factors associated with a good outcome included early response (odds ratio [OR] = 4.14), being employed, and the absence of physical comorbidities. Early remission was also strongly associated with a good outcome (OR = 4.72).

Conclusions: Either response or remission achieved by week 6 is the strongest prognostic factor for the 12-month good outcome of an episode of MDD.

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Major depressive disorder (MDD) is a common, disabling, and typically recurrent psychiatric condition that encompasses a broad range of emotional, psychological, behavioral, and physical symptoms.[1]

Previous clinical studies have examined baseline demographic, clinical, and social factors as predictors of outcome of major depression in adults. However, results have been inconsistent and even contradictory at times. Because most of those studies[2–4] were restricted to the analysis of short-term outcomes of the depressive episode, which do not adequately reflect the full course of the illness, depression should be viewed longitudinally rather than solely in terms of acute episodes.[5,6] In order to find more useful predictors of long-term outcome, researchers have turned to variables associated with early treatment response. The most widely studied is the presence of residual depressive symptoms after drug treatment for MDD, which has been consistently found to be associated with higher rates of relapse.[7–10] More recently, other treatment variables have been studied; Szádóczky et al[11] reported that the severity of depression at the end of a 2-year period can be predicted by the severity at the end of the 6-week acute treatment phase. Goldberg and Harrow[12] reported that the course of depression was predicted by the consistency of remission after the initial episode. Mulder et al[13] reported that early response was the most powerful predictor of outcome over 6 months.

Because of the recurrent and chronic course of depression, it is important to gather as much evidence as possible to study the maintenance of remission, which means more than just preventing relapses; it also means keeping the patient free of residual symptoms.[14] Predicting long-term outcomes at an early stage is highly relevant for treating MDD. If it were possible to predict the treatment outcome at an early stage, this might help physicians to determine a treatment approach to improve the chances of achieving remission and result in a better long-term outcome.[3]

The observation of a cohort of patients in real-world conditions over a long period of time would offer new and relevant information about the prognosis of MDD. We designed this 12-month follow-up study to test the hypothesis that response (and also remission) within the first 6 weeks of antidepressant treatment would be associated with a 12-month good outcome in the prognosis of a depressive episode.

METHOD

Study Design

During a period of 1 year, this prospective, longitudinal, multicenter, observational study assessed a cohort of outpatients with an index depressive episode who had begun follow-up for their current episode. Patients' information was collected 5 times: at baseline and at 4 follow-up visits (at 6 weeks and at 3, 6, and 12 months). At each visit, sociodemographic characteristics and relevant clinical information were obtained, and clinical scales and questionnaires were administered.

In accordance with the noninterventional nature of the study, psychiatrists did not receive any kind of treatment indications that might influence their usual practice patterns. Protocol was approved by the centers' ethics and research boards, and all participating patients provided written informed consent.

Eligibility Criteria

The study included adult outpatients diagnosed with nonpsychotic MDD, single or recurrent episode, according to the *DSM-IV-TR*[1] and who either had a minimum remission time period of 12 weeks between their index depressive episodes and the immediately prior episode or were in their first MDD episode. Patients had to have a baseline score ≥ 15 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[15,16] total score, a baseline score ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S) scale,[17] and experienced a change in treatment (dosage, type, or association of antidepressants) at baseline. Patients were excluded if they were on antidepressant treatment and had had any change in medication in the 12 weeks prior to the beginning of their index depressive episodes or if they were concomitantly participating in other studies. Patients who had an additional Axis I psychiatric disorder, dementia, Alzheimer's disease, organic brain syndrome, or cognitive impairment were excluded.

Efficacy Measures and Definitions

Response and remission were measured with the $HDRS_{17}$.[15,16] Other scales used were the CGI-S,[17] the Hamilton Anxiety Rating Scale (HARS),[18,19] and the visual analog scale (VAS) for pain.[20] Presence of personality disorders was evaluated with the Structured Clinical Interview for *DSM-IV* Axis II Disorders (SCID-II).[21,22]

Additionally, level of functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS),[23] considering scores > 80 as indicating an optimal level of functioning. Quality of life was assessed using the EQ-5D scale, scored according to United Kingdom norms.[24,25]

One of the key measures used in the study was early response, defined as 50% improvement on the $HDRS_{17}$ score versus baseline after the first 6 weeks of antidepressant treatment.

Early remission was defined as a patient's no longer meeting the criteria for MDD according to the *DSM-IV-TR* in addition to a $HDRS_{17}$ score ≤ 7 reached during the first 6 weeks of antidepressant treatment without any change of treatment during that period.

Patients were divided into 2 groups based on course of the illness: (1) a good outcome: determined by a patient's achieving remission in the first 6 months and remaining in remission until the end of follow-up (12 months) and (2) absence of a good outcome.

Statistical Analyses

A sample size of 860 patients achieved 80% power at a .05 2-sided significance level when performing a logistic regression of a binary response variable on a binary independent variable, assuming that 20% would have early response, to detect a change in probability (Y = 1) from the baseline value of 55%[13] to 71% of patients' achieving a good outcome. An adjustment was made because a multiple regression of the independent variable on the other independent variables in the logistic regression obtained an R^2 value of 0.250. It was assumed that approximately 30% of patients would drop out. Sample size estimation was calculated with Power Analysis and Sample Size 2000 software (NCSS, Kaysville, Utah).

Continuous variables were summarized using descriptive statistics and binary or categorical variables using absolute and relative frequencies. The primary exploratory analysis was to assess the prognostic value of early response by a multiple logistic regression model[26] with the dependent variable outcome (good versus not good) and the following possible risk factors as independent variables in the initial model:

- Early response
- Age, sex (male/female), marital status (married/other), and employment status (employed [including student or housewife]/other)
- Age at onset of illness
- Use of dual antidepressants (yes/no)
- Duration of actual episode (≤ 4 weeks/ 4–24 weeks/ ≥ 24 weeks)
- Family history of depression (yes/no)
- Previous episodes (yes/no)
- Baseline continuous scores of: $HDRS_{17}$, HARS, SOFAS, VAS (just item 1), and EQ-5D (United Kingdom norms)
- Physical comorbidities (yes/no)
- Psychiatric comorbidities measured by SCID-II (yes/no)
- Stressful life events (yes/no)

Clinical Points

- Potential predictors of clinical outcome of major depression in adults have been studied with inconclusive results. The observation of cohorts of patients in real-world conditions over a long period of time would offer new and relevant information about the prognosis of the illness.
- In this study, early (within 6 weeks) response and remission were strongly associated with a good outcome in the clinical course of major depression at 12-month follow-up; other factors associated with a good outcome were being employed and the absence of physical comorbidities.
- Furthermore, having early response and remission had a strong association with better social and occupational functionality and, in the case of early response, also with better quality of life.

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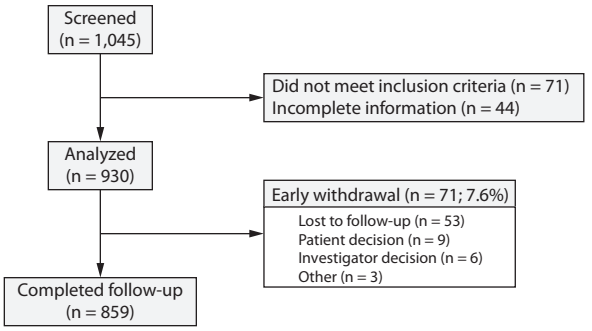
Figure 1. Patient Disposition



All the independent variables were included in a full model and then removed by stepwise backward selection (threshold for the *P* value = .05). The reduced model was reported in terms of odds ratios (ORs) and their 95% confidence intervals; the fit of the final model was assessed using the Hosmer-Lemeshow goodness-of-fit test.[27]

All models were performed on the completer's population as well as the entire study population according to the following assumptions: (1) early response—patients with no evaluation of the $HDRS_{17}$ at 6 weeks were considered nonresponders and (2) outcome—patients withdrawing before the end of 1-year follow-up were considered not to have a good outcome.

Results were similar in both populations; results in the whole population are reported, as they seemed more conservative (smaller OR).

The secondary analysis, impact of early remission on 12-month outcome, was assessed using the same modeling approach. The changes in SOFAS and EQ-5D scores were analyzed by an analysis of covariance (ANCOVA), which included the change in the score as the dependent variable, early response or not as factors, and the baseline value as a covariate, as well as sex, level of education, employment status, physical comorbidities, age, and baseline $HDRS_{17}$ and HARS scores. The same model was used to explore the effect of early remission on functioning.

Descriptive post hoc analyses were done on the first-episodes population including first episode indicator variable (yes/no) in the logistic regression models.

The statistical software package used to perform statistical analyses was SAS 9.2 for Windows (SAS Institute, Cary, North Carolina).

RESULTS

Patient Disposition, Demographic Characteristics, and Clinical Characteristics

From December 2006 to June 2007, 1,045 patients were screened. Of these, 930 were included, and of these, 859 (92.4%) completed the study (Figure 1). Demographic and clinical parameters are detailed in Table 1. The primary analysis was the association between early response and 12-month outcome.

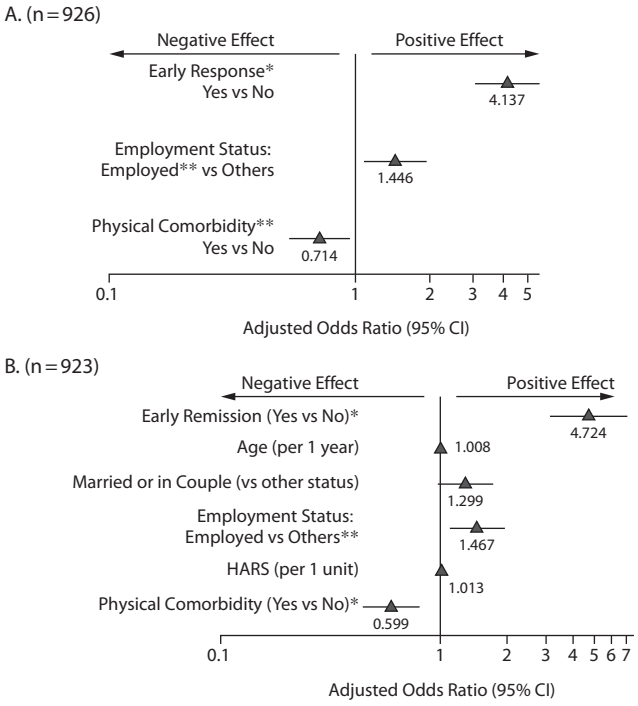
Table 1. Baseline Demographic and Clinical Characteristics of Patients (N = 930) With a Major Depressive Episode

Characteristic	Value
Age, mean (SD), y	47.1 (13.5)
Sex, n (%)	
Female	631 (67.9)
Ethnicity, n (%)	
White	909 (97.7)
Marital status, n (%)	
Married	559 (60.1)
Single	214 (23.0)
Widowed	53 (5.7)
Separated	104 (11.2)
Education, n (%)	
Basic studies	469 (50.4)
High school	267 (28.7)
Advanced studies	194 (20.9)
Employment status, n (%)	
Active	585 (62.9)
Disabled worker	209 (22.5)
Not working	72 (7.7)
Retired	63 (6.8)
Other	1 (0.1)
Family psychiatric history, n (%)	318 (34.2)
Patients with physical comorbidity, n (%)	503 (54.1)
Patients with personal psychiatric history, n (%)	129 (13.9)
Patients with first episode, n (%)	413 (44.4)
Current depressive episode:	
Duration of current episode, mean (SD), wk	14.2 (22.2)
Chronicity of current episode[a] ≥ 2 years, n (%)	57 (6.1)
Patients who received previous treatments for index episode, n (%)	332 (35.7)
Comorbid personality disorders, n (%)	163 (17.5)
Treatments, n (%)	
Monotherapy	815 (87.6)
Duloxetine	471 (50.7)
SSRI	204 (21.9)
Venlafaxine	115 (12.4)
Tricyclic antidepressants	9 (1.0)
Others	16 (1.7)
Combination of antidepressants	115 (12.4)
Age at first episode, mean (SD), y	40.04 (14.0)
Previous depressive episode:	
Number of previous episodes,[a,b] mean (SD), no.	2.5 (2.4)
Duration of last episode,[a,c] mean (SD), wk	24.5 (20.6)
Time from the beginning of current episode and remission of last episode,[d] mean (SD), wk	155.7 (217.4)
Resistance to treatment,[b] n (%)	80 (15.7)
Seasonal profile,[a,e] n (%)	46 (28.6)

[a]Calculated only for patients with 3 or more depressive episodes.
[b]n = 509.
[c]n = 505.
[d]n = 507.
[e]n = 161.
Abbreviations: MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor.

Among the 930 patients included, 355 (38.2%) showed early response and, among them, 76.1% had a good outcome versus 43.3% in the group of patients without early response. The logistic regression model for evaluating the factors associated with good outcome (Figure 2A) showed that early response (OR = 4.14; 95% CI = 3.07–5.57), being employed (OR = 1.45; 95% CI, 1.09–1.93), and a lack of physical comorbidities (OR = 0.71; 95% CI, 0.54–0.95) had an effect on outcome. The OR for early response indicates that, for early responders, the chance of achieving a good outcome after 1 year is 4.14 times higher than for those who did not achieve early response.

Figure 2. Logistic Regression Factors Significantly Related to 12-Month Outcome Using Early Response (A) and Early Remission (B) as Risk Factors



*$P < .0001$.
**$P < .05$.
Abbreviation: HARS = Hamilton Anxiety Rating Scale.

Association Between Early Remission and 12-Month Outcome

Of the 355 early responders, 191 (53.8%; 20.5% of the total population [N = 930]) also had early remission, and 81.1% of those demonstrated a good outcome versus 70.1% of those patients with early response but not early remission. This logistic model generated similar responses to the primary analysis; the factors that were significantly associated with good outcome (Figure 2B) were early remission (OR = 4.72; 95% CI, 3.17–7.05), being employed (OR = 1.47; 95% CI, 1.10–1.96), and the absence of physical comorbidities (OR = 0.60; 95% CI, 0.45–0.80).

Association Between Early Response/Remission and Functioning

The ANCOVA showed that early response had the strongest influence ($F = 41.3$, $P < .0001$) of all the variables assessed, as shown in Figure 3A and 3B (F value). When adjusting for all the other variables, patients with early response had a mean (slope estimation) improvement in functionality (SOFAS) of 32.8 (0.6) points compared with 27.3 (0.5) points in patients who did not achieve early response ($P < .0001$).

While repeating the ANCOVA using early remission instead of early response, it was found that early remission ($F = 23.9$, $P < .0001$) also had a strong association with functionality. Patients with early remission had a mean (slope estimation) improvement in functionality (SOFAS) scores of 34.7 (0.80) points, compared with 28.7 (0.41) points in patients who did not achieve early remission ($P < .0001$; Figure 3C and 3D).

Raw mean (SD) level of functioning (SOFAS) scores improved from baseline 52.3 (12.4) points during the 12-month follow-up period, reaching mean values within the normal range of > 80 (82.1 [11.3]) points. When comparing functioning in patients who had reached early response versus those who had not, we observed that, for those patients with early response, functioning, in mean values, increased earlier and reached the normal range in 3 months. The data differentiating patients with or without early remission reveal an even larger difference—patients with early remission reached the normal range as early as 6 weeks, whereas patients without early remission took up to 1 year to achieve the same goal (Figure 3A, 3B, 3C, and 3D).

Association Between Early Response and Quality of Life

The mean (SD) level of quality of life (EQ-5D) improved from a value of 0.23 (0.33) at baseline to 0.85 (0.23) at endpoint after 1 year. When analyzing the change in the EQ-5D scores, we observed clear differences between early responders and nonearly responders (Figure 4). In the ANCOVA performed to analyze the factors associated with a better quality of life (EQ-5D scale), an association was found with early response ($F = 19.0$, $P < .0001$), male sex ($F = 7.4$, $P = .0066$), and lower baseline scores on the $HDRS_{17}$ ($F = 18.3$, $P < .0001$), HARS ($F = 10.6$, $P = .0012$), and EQ-5D ($F = 93.4$, $P < .0001$).

Post Hoc Analysis of Patients Experiencing First MDD Episodes

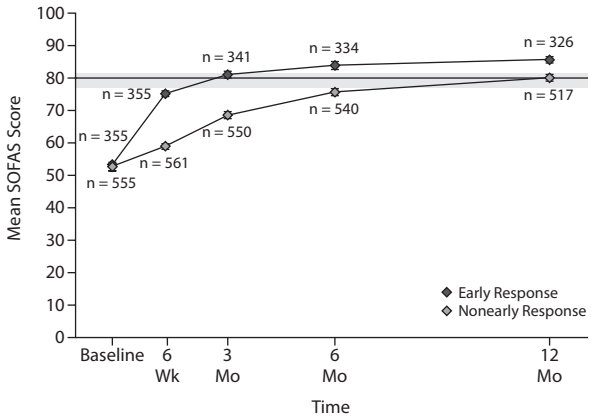
Due to the high percentage of patients experiencing first episodes of MDD (44.4%), we performed a post hoc analysis of patient characteristics in order to explore whether there was any difference between those patients and patients who had experienced previous episodes. No significant differences were found between these 2 cohorts.

DISCUSSION

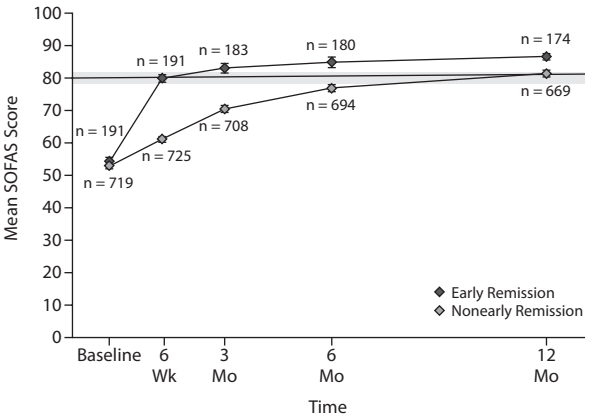
This longitudinal study of a large cohort of outpatients with MDD has provided the first evidence showing the effect of early clinical results measured in terms of response or remission in the prediction of 12-month outcome and normal functioning. The logistic regression analysis, with a good or not good outcome as the dependent variable, showed that early response or early remission (when this was used as an independent variable), being employed, and the absence of physical comorbidities are the factors that have a statistically significant positive effect on the 12-month outcome. Half of the patients who experienced early response also achieved early remission, and the majority of patients who showed early remission had a good outcome. In the present study, level of functioning, as measured by the SOFAS scale, was highly associated with early remission. Patients with early remission showed average normal functioning

Figure 3. Association Between Early Response/Remission and Functioning as Reflected in Social and Occupational Functioning Assessment Scale (SOFAS) Scores

A. Mean SOFAS Scores (raw values) Over Time by Early or Nonearly Response



C. Mean SOFAS Scores (raw values) Over Time by Early or Nonearly Remission



B. ANCOVA Analysis of the Mean Changes in SOFAS Scores (slope estimation) Using Early Response

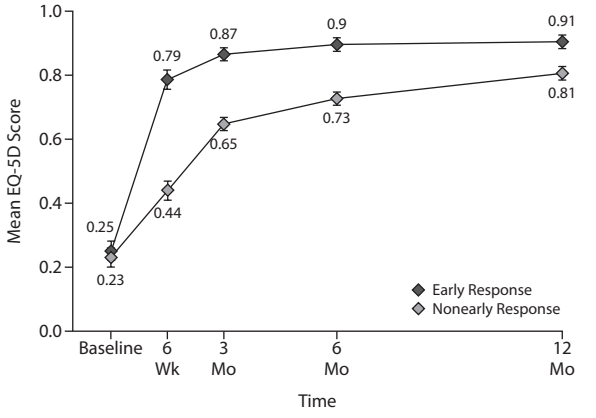
Variable	*F* Value	*P* Value	Estimate[a]
Early Response (N = 836)	41.3	< .0001	21.341
Employment status	28.6	< .0001	5.192
Early response*baseline SOFAS score	17.0	< .0001	−0.267
Baseline SOFAS score	10.8	.0010	−0.428
Physical comorbidity	10.6	.0012	−2.402
Baseline $HDRS_{17}$ score	7.7	.0057	0.672
Baseline $HDRS_{17}$ score*baseline SOFAS score	6.1	.0141	−0.012
Early response*employment status	5.3	.0215	−3.708
Sex	4.5	.0336	1.695

D. ANCOVA Analysis of the Mean Changes in SOFAS Scores (slope estimation) Using Early Remission

Variable	*F* Value	*P* Value	Estimate[a]
Early remission (N = 836)	23.9	< .0001	19.665
Employment status	10.3	.0014	10.661
Early remission*baseline SOFAS score	12.4	.0004	−0.260
Baseline SOFAS score	148.7	< .0001	−0.681
Physical comorbidity	14.8	.0001	−2.859
Baseline $HDRS_{17}$ score	3.5	.0623	0.144
Early remission*baseline SOFAS score	12.4	.0004	−0.260
Employment status*baseline SOFAS score	4.1	.0426	−0.130
Sex	7.9	.0051	2.243

[a]Slope estimation.
*Indicates interaction.
Abbreviations: ANCOVA = analysis of covariance, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

Figure 4. Mean EQ-5D Scores Over Time by Early or Nonearly Response (raw values)



as early as 6 weeks, whereas those without early remission needed the whole follow-up year to regain average normal functioning.

This topic is relatively new in the field of MDD management, and the number of relevant studies is still limited. Traditionally, most studies assess response at the eighth week of treatment and assess remission at the same time or even later. However, most recent studies and meta-analyses have focused on demonstrating that early improvement, as early as 2 weeks into antidepressant treatment, has consequences for response rate measured at short-term outcomes.[2,28–33] Nevertheless, the association between early response and/or remission and a good long-term outcome has not been adequately investigated until now. Our study is the first to explore the relation between reaching an early response (and even more important, an early remission) and the patients' outcomes 1 year later.

Predictors of the long-term outcomes of a depressive episode have been difficult to study,[34,35] although residual symptoms have been identified as the most consistent predictor of relapse. In this sense, early response has already been identified as a powerful predictor of outcome over 6 months.[13] Our results confirm the findings of Mulder et al[13] and even improve on them by showing that an early response at 6 weeks is the strongest predictor of a good 12-month prognosis, along with being employed and the absence of physical comorbidities. Furthermore, a patient who achieves remission at 6 weeks has an even better prognosis than one who has only achieved response by that time, when all other factors included in the analyses are the same. To our

knowledge, this is the first time that early remission has been shown to be a predictive factor for a good long-term outcome, which is ultimately the goal of treatment.

The World Health Organization defines the aim of treating patients with depression as returning them to a state of health, as "a state of complete physical, mental and social well-being and not merely the absence of disease."[36(p1)] Remission is considered the optimal outcome for a depressive episode and equivalent to the concept of health recovery.[30,37] Social functioning is thought to be associated with full remission,[38] symptomatic recovery,[39] and early symptom improvement.[4] In the present study, patients who achieved early response reached normal functioning at 3 months. Moreover, on average, patients with early remission reached normal functioning by week 6 of treatment.

The number of previous depressive episodes has been postulated as a predictive factor for long-term outcome.[8] Nevertheless, in the regression analysis developed in our study, the presence of previous episodes was not found to influence the long-term outcome. Another factor identified as a predictor in previous studies is the presence of personality disorders.[13] In light of this, we attempted to identify these types of disorders using a specific tool like the SCID-II in order to provide a more sound methodology. However, in our analysis personality disorders did not appear to be a predictor of the course of the illness.

The current study has some limitations. The study population could be considered to be a good-prognosis group due to the high number of patients with first episodes, the low proportion of patients having received prior treatment for an index episode, and the low mean duration of that treatment. Nevertheless, no differences were found when comparing the first-episodes sample with the nonfirst-episodes sample. Another limitation of this study is that, although there is recent evidence that early improvement at the second week is a very sensitive predictor of later response and remission,[2,29] we did not measure this variable. However, we were able to capture response and, for the first time, remission, as early as week 6. Evaluating early response at 6 weeks can be controversial, but according to the American Psychiatric Association,[39] the recommended time frame for the assessment of degree of response (ie, no response, partial response, and complete response) is between 4 to 8 weeks after the start of antidepressant treatment.[4] In our study, around 70% of patients were being treated with dual antidepressants, which usually need a titration period of about 1–2 weeks. Therefore, at the point these patients started taking the effective dose of antidepressant treatment, they had in fact only been treated for approximately 4 weeks, not 6.

So, from a clinical perspective, our analysis can be useful to clinicians in formulating treatment decisions for their patients in order to achieve better outcomes as soon as possible, while shortening the time spent on unsatisfactory treatments and consequently allowing them to decide when to adopt more effective therapeutics strategies.[2] In order for physicians to optimize their treatment approaches, there is a need for prospective randomized clinical trials designed to compare the implications of different treatment modifications at an early stage if response or remission is not achieved.

CONCLUSIONS

Early response and remission are the strongest prognostic factors for the 12-month good outcome of an episode of major depressive disorder in a 1-year follow-up period. Other factors involved were having an active employment status and the absence of physical comorbidities. Reaching early remission is also associated with normal functioning at the same time frame in which this early remission is reached (6 weeks). In order to facilitate better patient outcomes, it is important not only to achieve remission but also to achieve it as soon as possible, thus preventing patients from relapsing, alleviating their chronic symptoms, and allowing them to regain normal functioning.

Drug names: duloxetine (Cymbalta), venlafaxine (Effexor and others).
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Potential conflicts of interest: **Drs Ciudad**, **Casillas**, **Valladares**, and **Gilaberte** and **Ms García de Polavieja** are full-time employees of Lilly Spain. **Drs Álvarez**, **Baca**, and **Caballero** have served on advisory boards for Eli Lilly. **Dr Roca** has served on advisory boards for Wyeth and Eli Lilly.
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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Publishing; 2000.
2. Tadić A, Helmreich I, Mergl R, et al. Early improvement is a predictor of treatment outcome in patients with mild major, minor or subsyndromal depression. *J Affect Disord*. 2010;120(1–3):86–93.
3. Wade AG, Schlaepfer TE, Andersen HF, et al. Clinical milestones predict symptom remission over 6-month and choice of treatment of patients with major depressive disorder (MDD). *J Psychiatr Res*. 2009;43(5):568–575.
4. Papakostas GI, Petersen T, Denninger JW, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. *J Clin Psychopharmacol*. 2004;24(5):507–511.
5. Kelsey JE. Clinician perspective on achieving and maintaining remission in depression. *J Clin Psychiatry*. 2001;62(suppl 26):16–21.
6. Mulder RT, Frampton CM, Luty SE, et al. Eighteen months of drug treatment for depression: predicting relapse and recovery. *J Affect Disord*. 2009;114(1–3):263–270.
7. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25(6):1171–1180.
8. Pintor L, Torres X, Navarro V, et al. Is the type of remission after a major depressive episode an important risk factor to relapses in a 4-year follow up? *J Affect Disord*. 2004;82(2):291–296.
9. 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(2–3):97–108.
10. Prien RF, Kupfer DJ. Continuation drug therapy for major depressive episodes: how long should it be maintained? *Am J Psychiatry*. 1986;143(1):18–23.
11. Szádóczky E, Rózsa S, Zámbori J, et al. Predictors for 2-year outcome of major depressive episode. *J Affect Disord*. 2004;83(1):49–57.
12. Goldberg JF, Harrow M. Consistency of remission and outcome in bipolar and unipolar mood disorders: a 10-year prospective follow-up. *J Affect Disord*. 2004;81(2):123–131.
13. Mulder RT, Joyce PR, Frampton CM, et al. Six months of treatment for depression: outcome and predictors of the course of illness. *Am J Psychiatry*. 2006;163(1):95–100.
14. Thase ME. Achieving remission and managing relapse in depression. *J Clin Psychiatry*. 2003;64(suppl 18):3–7.
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
16. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
17. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* US Dept Health, Education, & Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychiatry.* 1959;32(1):50–55.
19. Riskind JH, Beck AT, Brown G, et al. Taking the measure of anxiety and depression: validity of the reconstructed Hamilton scales. *J Nerv Ment Dis*. 1987;175(8):474–479.
20. DeLoach LJ, Higgins MS, Caplan AB, et al. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg*. 1998;86(1):102–106.
21. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II),* version 2.0. New York, NY: New York State Psychiatric Institute, Biometrics Research Department; 1994.
22. Maffei C, Fossati A, Agostoni I, et al. Interrater reliability and internal consistency of the structured clinical interview for *DSM-IV* Axis II personality disorders (SCID-II), version 2.0. *J Pers Disord*. 1997;11(3): 279–284.
23. Goldman HH, Skodol AE, Lave TR. Revising Axis V for *DSM-IV*: a review of measures of social functioning. *Am J Psychiatry*. 1992;149(9): 1148–1156.
24. [No authors listed]. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*. 1990; 16(3):199–208.
25. Sobocki P, Ekman M, Agren H, et al. Health-related quality of life measured with EQ-5D in patients treated for depression in primary care. *Value Health*. 2007;10(2):153–160.
26. Lee J. An insight on the use of multiple logistic regression analysis to estimate association between risk factor and disease occurrence. *Int J Epidemiol*. 1986;15(1):22–29.
27. Hosmer DW, Lemeshow S. A goodness-of-fit test for the multiple logistic regression model. *Commun Stat Theory Methods*. 1980;9(10): 1043–1069.
28. van Calker D, Zobel I, Dykierek P, et al. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. *J Affect Disord*. 2009;114(1-3):243–253.
29. Henkel V, Seemüller F, Obermeier M, et al. Does early improvement triggered by antidepressants predict response/remission? analysis of data from a naturalistic study on a large sample of inpatients with major depression. *J Affect Disord*. 2009;115(3):439–449.
30. Nakajima S, Suzuki T, Watanabe K, et al. Accelerating response to antidepressant treatment in depression: a review and clinical suggestions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(2):259–264.
31. Lutz W, Stulz N, Köck K. Patterns of early change and their relationship to outcome and follow-up among patients with major depressive disorders. *J Affect Disord*. 2009;118(1-3):60–68.
32. Szegedi A, Jansen WT, van Willigenburg AP, et al. Early improvement in the first 2 *w*eeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry*. 2009;70(3):344–353.
33. Dawson MY, Michalak EE, Waraich P, et al. Is remission of depressive symptoms in primary care a realistic goal? a meta-analysis. *BMC Fam Pract*. 2004;5:19.
34. Holma KM, Holma IA, Melartin TK, et al. Long-term outcome of major depressive disorder in psychiatric patients is variable. *J Clin Psychiatry*. 2008;69(2):196–205.
35. Pettit JW, Lewinsohn PM, Roberts RE, et al. The long-term course of depression: development of an empirical index and identification of early adult outcomes. *Psychol Med*. 2009;39(3):403–412.
36. World Health Orgnization. Constitution. Geneva, Switzerland; 1946. http://apps.who.int/gb/bd/PDF/bd47/EN/constitution-en.pdf.
37. Trivedi MH. Tools and strategies for ongoing assessment of depression: a measurement-based approach to remission. *J Clin Psychiatry*. 2009;70(suppl 6):26–31.
38. Romera I, Perez V, Menchón JM, et al. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode: a six-month prospective epidemiological study. *Eur Psychiatry*. 2010;25(1):58–65.
39. Furukawa TA, Takeuchi H, Hiroe T, et al. Symptomatic recovery and social functioning in major depression. *Acta Psychiatr Scand*. 2001;103(4):257–261.
40. American Psychiatric Association APA. (2004). Treating major depressive disorder: a quick reference guide. http://www.psychiatryonline.com/pracGuide/PracticePDFs/MDD2e_QRG.pdf.