Early Improvement in the First 2 Weeks as a Predictor of Treatment Outcome in Patients With Major Depressive Disorder: A Meta-Analysis Including 6562 Patients

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Objective: New evidence indicates that treatment response can be predicted with high sensitivity after 2 weeks of treatment. Here, we assess whether early improvement with antidepressant treatment predicts treatment outcome in patients with major depressive disorder (MDD).

Data Sources: Forty-one clinical trials comparing mirtazapine with active comparators or placebo in inpatients and outpatients (all-treated population, N = 6907; intent-to-treat population, N = 6562) with MDD (DSM-III-R or DSM-IV Criteria) were examined for early improvement (≥ 20% score reduction from baseline on the 17-item Hamilton Rating Scale for Depression [HAM-D-17] within 2 weeks of treatment) and its relationship to treatment outcome.

Study Selection: Data were obtained from a systematic search of single- or double-blind clinical trials (clinical trials database, Organon, a part of Schering-Plough Corporation, Oss, The Netherlands). All included trials (a total of 41) employed antidepressant treatment for more than 4 weeks and a maximum of 8 weeks. The studies ranged from March 1982 to December 2003. Trials were excluded if there were no HAM-D-17 ratings available, no diagnosis of MDD, or if the study was not blinded. Trials were also excluded if HAM-D-17 assessments were not available at week 2, week 4, and at least once beyond week 4.

Data Synthesis: Early improvement predicted stable response and stable remission with high sensitivity (≥ 81% and ≥ 87%, respectively). Studies utilizing rapid titration vs. slow titration of mirtazapine demonstrated improved sensitivity for stable responders (98%, [95% CI = 93% to 100%] vs. 91% [95% CI = 89% to 93%]) and stable remitters (100%, [95% CI = 92% to 100%] vs. 93% [95% CI = 91% to 95%]). Negative predictive values for stable responders and stable remitters were much higher (range = 82%–100%) than positive predictive values (range = 19%–60%).

Conclusions: These results indicate that early improvement with antidepressant medication can predict subsequent treatment outcome with high sensitivity in patients with major depressive disorder. The high negative predictive values indicate little chance of stable response or stable remission in the absence of improvement within 2 weeks. A lack of improvement during the first 2 weeks of therapy may indicate that changes in depression management should be considered earlier than conventionally thought.

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When a patient with major depressive disorder (MDD) starts antidepressant drug treatment, the ability to identify as early as possible those people who will not benefit from a particular type of treatment could minimize unnecessary drug exposure, lessen suffering, and limit resource use. This ability in turn allows for earlier initiation of a treatment adaptation such as alternative or adjunctive treatment. The early identification of nonresponders is also important because selection of an antidepressant agent is still primarily guided by trial and error.

Although the current expert consensus indicates that antidepressants may have a rapid onset of action in some individuals,[1–4] most current treatment guidelines do not contain recommendations for adapting an individual's treatment during the early course of therapy (e.g., within the first 2 weeks of treatment). Rather, treatment guidelines reflect the outdated belief that antidepressant response usually appears with a delay of several weeks[5]

and suggest that treatment should be changed if a partial response has not occurred after 4 to 6 weeks.[6–10] This advice was reinforced by the perception that placebo-controlled trials do not usually show a significant effect of treatment before treatment week 3. This perception reflected the assumption that early improvement was indicative of a placebo response associated with an irregular time course of recovery.[11–13] To a large extent, these beliefs are no longer held by experts in the treatment community.[14] However, physicians who follow the most current treatment guidelines may not consider a medication change within the first 2 weeks of treatment to be a useful strategy for improving the management of depression.

Because most antidepressant treatment guidelines continue to suggest 4 to 6 weeks of treatment until nonresponse can be assumed, substantial patience and adherence is required from depressed patients, particularly when pessimism and hopelessness dominate the outlook of these patients. Ineffective treatment is especially problematic in depression because it can increase the risk that patients lose confidence in and detach from their treating physicians, stop taking their prescribed treatment, or lose hope that their symptoms can be effectively treated. As a result, the risk of serious complications, such as suicide, is increased. Clearly, early identification of patients who subsequently will not benefit from a longer course of antidepressant therapy has immense clinical significance.

The hypothesis that antidepressants have a delayed onset of action gained support from the way data from clinical trials are analyzed. Most trials, including pivotal trials used to demonstrate efficacy for regulatory authorities, use group comparisons to detect significant mean differences between the antidepressant and placebo. Using this analytic approach, statistically significant differences between effective antidepressants and placebo are usually detected after 3 to 4 weeks of treatment. This approach assumes that mean differences adequately reflect changes observed in the individual patient. However, an examination of data from individuals participating in antidepressant clinical trials reveals a high degree of variability between patients. This broad range of responses suggests that individual responsiveness may not be adequately represented by the assumption of the "average" patient.

The delayed-onset hypothesis for antidepressant action is now being challenged. Many studies have not only reported onset of antidepressant action within the first 2 weeks of treatment,[1–3,14–20] but have also substantiated a close relationship between improvement of depression symptoms within the first 2 weeks of treatment and the final treatment response.[16–20] For example, Stassen and colleagues[16–19] analyzed the time course of intraindividual treatment outcomes in patients with depression by means of survival analyses. In these studies, patients who improved during the first 2 weeks of antidepressant treatment, as indexed by a ≥ 20% reduction in score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), showed substantial response at the study endpoint, as indexed by a ≥ 50% reduction in HAM-D-17 score. Stassen and colleagues argued not only that early improvement predicted response at study endpoint but also that lack of improvement was associated with little chance of response if the treatment strategy remained unchanged. It is important to note that the criterion of a 20% score reduction has been chosen as an early indicator of improvement because it can be reliably measured in clinical trials and translates into a clinically relevant change in the severity of depressive symptoms in patients (e.g., for a moderately depressed patient with an initial HAM-D-17 score of 20 points, it means a decrease of 4 points). However, a change of 20% is not a sensible target for therapeutic intervention and should not be understood as such.

As early as 1987, Katz et al.[21] reported that the onset of improvement occurred within the first 10 days of treatment across several domains in hospitalized patients with MDD who were being treated with a tricyclic antidepressant (TCA). This study did not include a placebo control group; thus, it could be questioned whether the early clinical treatment effects observed were due to drug effects or placebo effects. This issue was addressed in a subsequent randomized, parallel-group, placebo-controlled study in which patients were treated with the selective serotonin reuptake inhibitor (SSRI) paroxetine or the norepinephrine reuptake inhibitor desipramine.[4] In this study, early treatment-specific behavioral changes were demonstrated that were not observed in the placebo-treated group, and these early changes were highly predictive of ultimate clinical responses to antidepressant therapy. It was argued that these results could eventually be directly applied to clinical practice. Nierenberg and colleagues[15] have also reported that more than 50% of patients who eventually responded to fluoxetine treatment started to improve during the first 2 weeks of treatment. This same group has also reported that early nonresponse to fluoxetine treatment predicted poor 8-week outcomes.[22] Clearly, evidence continues to accumulate that indicates early individual improvement is a key predictor of treatment response.

In 2003, Szegedi et al.[20] examined early improvement with antidepressant treatment in a randomized controlled trial comparing mirtazapine and paroxetine in patients with a *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis of major depression. Improvement occurred in a majority of patients within 2 weeks of initiating treatment, and this improvement was a highly sensitive predictor of later stable response or stable remission for both drugs. Furthermore, negative predictive value approached maximal values as early as week 2 for

mirtazapine and week 3 for paroxetine. Less than 10% of patients who had not improved after 2 weeks of treatment became stable responders or remitters over the course of the study. These results indicate that response or nonresponse to antidepressant treatment can be predicted with high sensitivity after 2 weeks of therapy. Clearly, such findings could have significant clinical relevance if applied in clinical practice. The capacity to predict outcome during the early stages of treatment could not only shorten the length of ineffective treatments but could also decrease morbidity, mortality, and resource use associated with prolonged depression.

In the report by Szegedi et al.,[20] several caveats were considered in regard to interpretation of their data. First, the sample consisted primarily of moderately depressed outpatients. Although it was noted that this population was representative of the patients typically encountered in primary care settings and that their conclusions were fully appropriate for that patient population, it was unclear if the conclusions could be generalized to more severely depressed patients. Second, the results were confined to mirtazapine and paroxetine, so it was unclear if the results could be generalized to other antidepressants. Third, the lack of a placebo group in this study limited the ability to generalize these observations.[16]

The objective of the present study was to confirm the findings of Szegedi et al.[20] in a large patient population with MDD. Data from 6562 patients with MDD who participated in randomized, single- or double-blind clinical trials comparing mirtazapine with active comparators or placebo from March 1982 to December 2003 were retrospectively examined to determine the time course of improvement, response, and remission in individual patients, as well as the predictive capacity of early improvement for later treatment outcome.

METHOD

Inclusion of Studies

Analyses were carried out using data obtained from a systematic search of single- or double-blind clinical trials (clinical trials database; Organon, a part of Schering-Plough Corporation, Roseland, N.J.) comparing mirtazapine with active comparators or placebo in patients with MDD. The studies ranged from March 1982 to December 2003. The algorithm for trial selection is provided in Figure 1. Trials were excluded if there were no HAM-D-17 ratings available, no diagnosis of MDD, or if the study was not blinded. Trials were also excluded if HAM-D-17 assessments were not available at week 2, week 4, and at least once beyond week 4.

Patient Population

All patients met DSM-III-R or DSM-IV criteria for the diagnosis of at least 1 major depressive episode. The HAM-D-17 total score was used to assess the baseline severity of depressive symptoms (mild = < 22; moderate = 22–25; severe = > 25). Each study was approved by the institutional review board for the participating site. Written informed consent was obtained from all participants prior to participation in the original clinical trials and all studies were conducted in compliance with the current revision of the Declaration of Helsinki.

Outcome Measures

For the purpose of this analysis, the following patient groups were defined:

1. Early improvers: patients having a reduction in HAM-D-17 score of ≥ 20% compared with baseline within the first 2 weeks of treatment. This threshold represents a clinically meaningful change in the patient's state and can be reliably assessed.
2. Treatment responders: patients having a reduction in HAM-D-17 score of ≥ 50% from baseline.
3. Stable responders: patients having a reduction in HAM-D-17 score of ≥ 50% from baseline at 4 weeks of treatment and at all subsequent assessments.
4. Symptom remitters: patients having a reduction in HAM-D-17 score to ≤ 7 points.
5. Stable remitters: patients having a reduction in HAM-D-17 score to ≤ 7 points at week 4 of treatment and at all subsequent assessments.

Statistical Analyses

Analyses of the predictive value of early response for stable response and remission at 4 weeks were performed on the intent-to-treat (ITT) population. The method of last observation carried forward (LOCF) was used for missing values. The number of early improvers, responders, stable responders, remitters, and stable remitters was entered into a contingency table. The following indices, as well as their respective 95% Fisher exact CIs, were then calculated:

1. Sensitivity: [Early improvers who became stable responders or stable remitters/(Early improvers who became stable responders or stable remitters + Early nonimprovers who became stable responders or stable remitters)] × 100.
2. Specificity: [Early nonimprovers who did not become stable responders or stable remitters/(Early nonimprovers who did not become stable responders or stable remitters + Early improvers who did not become stable responders or stable remitters)] × 100.
3. Positive predictive value: (Early improvers who became stable responders or stable remitters/All improvers) × 100.

4. Negative predictive value (Early nonimprovers who did not become stable responders or stable remitters/All nonimprovers) × 100.
5. False positives: 100% – Specificity.
6. False negatives: 100% – Sensitivity.

All statistical analyses were performed using SAS analytic software (SAS Institute Inc., Cary, N.C.).

RESULTS

Studies Included

A total of 145 trials were identified (Figure 1). Trials were excluded from the analysis if there were no HAM-D-17 ratings (N = 71), no MDD diagnosis (N = 3), or if the study was not blinded (N = 19). An additional 11 trials were excluded because a valid HAM-D-17 assessment was not available at week 2, week 4, and at least once beyond week 4.

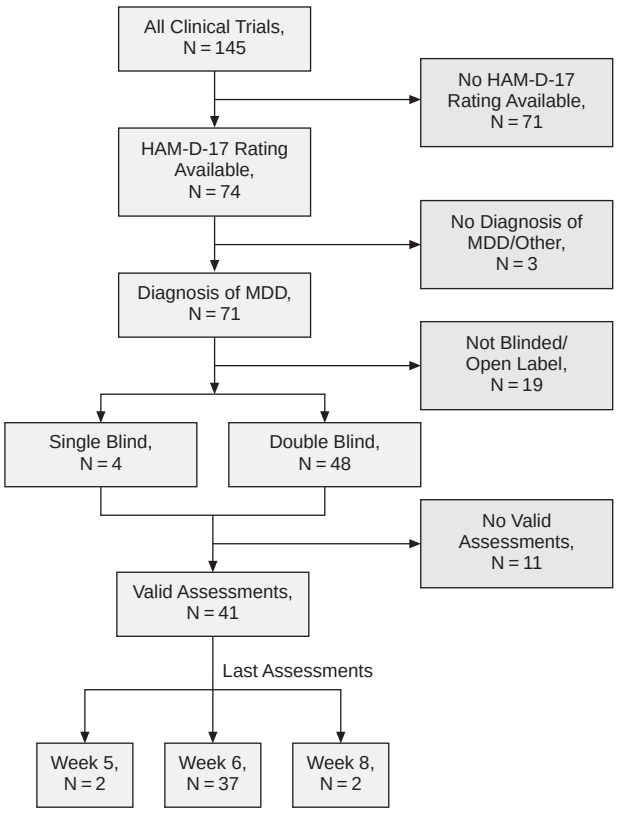
A total of 41 single- or double-blind clinical trials in patients with MDD were included in the analyses. The majority consisted of a 6-week antidepressant treatment period (N = 37). The remaining trials consisted of 5-week (N = 2) or 8-week (N = 2) antidepressant treatment periods. All studies used common inclusion/exclusion criteria, but varied in the criterion for depression severity required for enrollment.

Demographic Characteristics

The all-treated and ITT populations consisted of 6907 and 6562 patients, respectively. Demographic characteristics for the ITT population are presented in Table 1. As indexed by mean HAM-D-17 scores, a majority of patients (68%) met criteria for moderate or severe depression at baseline. In 20 studies, data on previous episodes of depression were available; the majority of patients (63%) in these studies had a history of previous episodes of depression. In 27 studies, data on the duration of current MDD were available. In these studies, the duration of the current MDD exceeded 1 month in more than 90% of patients (< 1 month, 9%; 1–6 months, 44%; 6 months to 1 year, 20%; > 1 year, 27%).

The noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine was used in all studies. The classes of antidepressants that were active comparators included the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine; the SSRIs (paroxetine, fluoxetine, citalopram, sertraline, and fluvoxamine); the TCAs (amitriptyline, doxepin, and clomipramine); the tetracyclic antidepressant maprotiline, and trazodone (chemically unrelated to other antidepressants). Fifty-two percent of patients were taking mirtazapine. The percentages of patients taking other antidepressants or placebo were SSRI = 21%; TCA = 11%; placebo = 10%; trazodone or maprotiline = 4%; and venlafaxine = 3%. In 2 trials that focused on rapid dose titration, mirtazapine and venlafaxine were studied head to head. The results from these 2 trials for mirtazapine patients (3% of the all-treated population) are also discussed.

Figure 1. Systematic Review of Clinical Trials[a]



[a]A total of 145 clinical trials from March 1982 to December 2003 were reviewed for inclusion in the analyses. Trials were systematically excluded from the analysis if there were no HAM-D-17 ratings, no diagnosis of MDD, if the study was not blinded, and if the study did not have a HAM-D-17 assessment at week 2, week 4, and at least once beyond week 4.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder.

Treatment Response

The majority of patients had at least a 20% reduction in HAM-D-17 total score by week 2 of treatment (Table 2). Of these, the highest proportion of improvers was observed across all weeks for patients who had rapid titration with mirtazapine.

The numbers of responders, stable responders, remitters, and stable remitters across treatment weeks demonstrate that responses to treatment follow a similar time course (Table 3). More than one half of patients taking active treatment became stable responders, and more than one third of patients taking active treatment became stable remitters at the end of treatment.

Table 1. Demographic Characteristics at Baseline for the Intent-to-Treat Population[a]

Characteristic	Placebo	Mirtazapine	Venlafaxine	SSRI	TCA	Other[b]	Total
Sex							
Male	394 (62)	2084 (61)	118 (62)	844 (61)	487 (69)	160 (68)	4087 (62)
Female	244 (38)	1318 (39)	72 (38)	535 (39)	217 (31)	77 (33)	2463 (38)
Data unavailable	3 (1)	4 (< 1)	0 (0)	0 (0)	5 (1)	0 (0)	12 (< 1)
Race							
Asian	4 (1)	178 (5)	0 (0)	167 (12)	3 (< 1)	1 (< 1)	353 (5)
Black	30 (5)	71 (2)	0 (0)	27 (2)	5 (1)	0 (0)	133 (2)
White	509 (79)	1790 (53)	116 (61)	845 (61)	268 (38)	45 (19)	3573 (54)
Other	22 (3)	55 (2)	0 (0)	26 (2)	4 (1)	1 (< 1)	108 (2)
Data unavailable	76 (12)	1312 (39)	74 (39)	314 (23)	429 (61)	190 (80)	2395 (37)
Age, y							
< 18	85 (13)	165 (5)	0 (0)	0 (0)	0 (0)	0 (0)	250 (4)
18–24	39 (6)	156 (5)	10 (5)	105 (8)	28 (4)	3 (1)	341 (5)
25–44	284 (44)	1393 (41)	79 (42)	595 (43)	295 (42)	67 (28)	2713 (41)
45–59	158 (25)	1129 (33)	81 (43)	442 (32)	248 (35)	111 (47)	2169 (33)
≥ 60	72 (11)	559 (16)	20 (11)	237 (17)	133 (19)	56 (24)	1077 (16)
Data unavailable	3 (1)	4 (< 1)	0 (0)	0 (0)	5 (1)	0 (0)	12 (< 1)
Mean (SD), y	38.9 (15.8)	44.3 (15.1)	44.5 (11.6)	45.3 (14.5)	47.3 (13.6)	50.4 (12.0)	44.5 (14.9)
HAM-D-17 total score, Mean (SD)	22.8 (4.3)	24.0 (4.7)	26.5 (3.5)	24.0 (4.3)	24.4 (4.7)	26.0 (4.9)	24.1 (4.6)
HAM-D-17 severity score							
Mild[c]	261 (41)	1145 (34)	10 (5)	429 (31)	208 (29)	45 (19)	2098 (32)
Moderate[d]	221 (35)	1085 (32)	71 (37)	482 (35)	236 (33)	66 (28)	2161 (33)
Severe[e]	158 (25)	1167 (34)	108 (56)	464 (34)	265 (37)	126 (53)	2288 (35)
Data unavailable	1 (< 1)	9 (< 1)	1 (1)	4 (< 1)	0 (0)	0 (0.0)	15 (< 1)

[a]All data presented as N (%) unless otherwise noted.
[b]Other = trazodone or maprotiline.
[c]Baseline HAM-D-17 total score < 22.
[d]Baseline HAM-D-17 total score ≥ 22 and ≤ 25.
[e]Baseline HAM-D-17 total score > 25.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Predictive Value of Early Improvement

The predictive values of early improvement for treatment outcome (stable response and stable remission) are presented in Table 4. Across all treatments, early improvement was a highly sensitive predictor of stable response (range = 81%–98%) and stable remission (range = 87%–100%). However, early improvement was not a highly *specific* predictor for stable response (range = 43%–60%) or stable remission (range = 30%–53%). Furthermore, negative predictive values for stable response (range = 82%–96%) and stable remission (range = 95%–100%) were higher than positive predictive values for these groups (ranges = 43%–60% and 19%–28%, respectively).

In the 2 head-to-head trials that focused on rapid dose titration, the predictive value of early improvement was enhanced (Table 4). In these studies, rapid dose titration of mirtazapine was associated with the highest sensitivity for predicting later stable responders (98%, 95% CI = 93% to 100%) and stable remitters (100%, 95% CI = 92% to 100%). These 2 studies also had the highest positive and negative predictive values for stable responders (60%, 95% CI = 52% to 68% and 96%, 95% CI = 86% to 100%, respectively) and stable remitters (28%, 95% CI = 21% to 36% and 100%, 95% CI = 93% to 100%), as well as the lowest false-negative rates (stable responder: 2%, 95% CI = 0.3% to 8%; stable remitter: 0%, 95% CI = 0% to 8%). A direct comparison of slow versus rapid dose titration for venlafaxine was not possible. However, rapid titration of venlafaxine was associated with high sensitivity for predicting later stable responders (96%, 95% CI = 89% to 99%) and stable remitters (100%, 95% CI = 89% to 100%), high positive and negative predictive values for stable responders (56%, 95% CI = 47% to 64% and 94%, 95% CI = 84% to 99%, respectively) and stable remitters (23%, 95% CI = 17% to 31% and 100%, 95% CI = 93% to 100%), and low false-negative rates (stable responder: 4%, 95% CI = 1% to 11%; stable remitter: 0%, 95% CI = 0% to 11%).

Outcomes of Early Improvement

We examined the percentage of early improvers and those without early improvement who later became stable responders (Figure 2) and stable remitters (Figure 3). By the end of treatment, 2285 (53%) early improvers were stable responders and 1084 (25%) were stable remitters. As such, early improvers constituted 90% (2285 of 2544) and 92% (1084 of 1177) of all stable responders and stable remitters, respectively. These results clearly show that patients who improve within the first 2 weeks of antidepressant therapy are highly likely to achieve stable response and stable remission after 4 weeks or longer of

Table 2. HAMD-17 Improvers[a] by Treatment Week for the Intent-to-Treat Population

Treatment, N (%)[b]	Week 1	Week 2	Week 3[c]	Week 4	Beyond Week 4
Placebo (N = 641)					
No	388 (69)	306 (48)	231 (41)	244 (38)	216 (34)
Yes	176 (31)	334 (52)	333 (59)	396 (62)	424 (66)
Mirtazapine (N = 3406)					
No	1415 (53)	1088 (32)	464 (25)	700 (21)	569 (17)
Yes	1240 (47)	2309 (68)	1414 (75)	2697 (79)	2828 (83)
Mirtazapine (rapid titration, N = 202)					
No	84 (42)	48 (24)	31 (25)	32 (16)	28 (14)
Yes	118 (58)	154 (76)	94 (75)	170 (84)	174 (86)
Venlafaxine (rapid titration, N = 190)					
No	100 (53)	52 (28)	28 (24)	43 (23)	37 (20)
Yes	89 (47)	137 (72)	87 (76)	146 (77)	152 (80)
SSRI (N = 1378)					
No	829 (63)	503 (37)	252 (31)	318 (23)	248 (18)
Yes	477 (37)	872 (63)	574 (69)	1057 (77)	1127 (82)
TCA (N = 709)					
No	251 (62)	219 (31)	66 (22)	137 (19)	103 (15)
Yes	153 (38)	490 (69)	240 (78)	572 (81)	606 (85)
Other[d] (N = 237)					
No	105 (64)	95 (40)	19 (29)	46 (19)	41 (17)
Yes	59 (36)	142 (60)	46 (71)	191 (81)	196 (83)

[a]Improvers were defined as having a ≥ 20% reduction in HAM-D-17 total score.
[b]Percentages are based on the total number of patients actually assessed at a given study week.
[c]Week 3 was not a scheduled assessment in all studies.
[d]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

continued treatment. In contrast, only 11% and 4.1% of patients, respectively, who did not improve within the first 2 weeks became stable responders or stable remitters. These results appear to be very robust. Similar analyses of early improvement predicting treatment response in data from a subset of patients for whom data from the Montgomery-Asberg Depression Rating Scale (MADRS) were available yielded similar results (data not presented).

DISCUSSION

The results of this analysis confirm that early improvement in depressive symptoms is frequently observed during the course of treatment with various antidepressant therapies, including mirtazapine, and that early improvement heralds a greater likelihood of stable response to medication and stable remission of symptoms. Importantly, the lack of early improvement is associated with low rates of medication response and symptom remission. These data thus provide further evidence against the delayed-onset hypothesis for antidepressant treatment response.[23–25] and further enforce the notion that an early improvement during treatment is expected with various antidepressant drugs. Thus a lack of early improvement may warrant the need for a change in treatment strategy. It should be noted that prospective and direct comparisons of response and remission rates in nonimprovers who continue treatment compared to those who changed treatment is needed to validate this recommendation. However, if found to be true, such an approach will have far-reaching implications for clinical practice.

The most immediate and practical consequence of this analysis is that a patient's individual early improvement may predict that individual's later stable response or remission with high sensitivity. Most prominently, a lack of early response to treatment at 2 weeks was highly predictive of a lack of stable response or stable remission. This is consistent with previous findings that indicated that the presence or absence of early improvement during mirtazapine or paroxetine treatment was highly predictive of therapeutic outcome.[20] In addition, in patients treated with *Hypericum* extracts, a reduction of depressive symptoms during the first 2 weeks of treatment was a sensitive predictor of sustained response.[26] The current analysis extends these findings to a variety of widely used antidepressants with different pharmacologic profiles. Furthermore, the finding that early individual improvement can predict sustained response is consistent with the finding that the response trajectory early during treatment is a useful predictor of response to antidepressants.[27] In fact, the criterion set forth in the current analysis (i.e., 20% improvement over 2 weeks) represents a favorable response trajectory.

It should be noted that there are important methodological differences between the approach of Quitkin and colleagues[13] and the strategy examined herein. Specifically, they measured outcome using the Clinical Global Impressions scale and required that patients be rated as "much improved" or "very much improved" to be counted as responders. In addition, they studied treatment with TCAs

Table 3. Responders[a] and Remitters[b] by Treatment Week for the Intent-to-Treat Population

	Responders					Stable Responders				
Treatment, N (%)	Week 1	Week 2	Week 3[d]	Week 4	Beyond Week 4	Week 1	Week 2	Week 3[d]	Week 4	Beyond Week 4
Placebo (N = 641)										
No	530 (94)	532 (83)	429 (76)	447 (70)	370 (58)	550 (98)	567 (89)	479 (85)	477 (75)	397 (62)
Yes	34 (6)	108 (17)	135 (24)	193 (30)	270 (42)	14 (2)	73 (11)	85 (15)	163 (25)	243 (38)
Mirtazapine (N = 3406)										
No	2372 (89)	2522 (74)	1168 (62)	1806 (53)	1349 (40)	2476 (93)	2721 (80)	1315 (70)	1984 (58)	1422 (42)
Yes	283 (11)	875 (26)	710 (38)	1591 (47)	2048 (60)	179 (7)	676 (20)	563 (30)	1413 (42)	1975 (58)
Mirtazapine (rapid titration, N = 202)										
No	164 (81)	118 (58)	64 (51)	91 (45)	79 (39)	167 (83)	135 (67)	73 (58)	108 (53)	84 (42)
Yes	38 (19)	84 (42)	61 (49)	111 (55)	123 (61)	35 (17)	67 (33)	52 (42)	94 (47)	118 (58)
Venlafaxine (rapid titration, N = 190)										
No	177 (94)	135 (71)	77 (67)	100 (53)	91 (48)	179 (95)	148 (78)	80 (70)	110 (58)	93 (49)
Yes	12 (6)	54 (29)	38 (33)	89 (47)	98 (52)	10 (5)	41 (22)	35 (30)	79 (42)	96 (51)
SSRI (N = 1378)										
No	1215 (93)	1080 (79)	571 (69)	812 (59)	542 (39)	1246 (95)	1160 (84)	636 (77)	884 (64)	571 (42)
Yes	91 (7)	295 (21)	255 (31)	563 (41)	833 (61)	60 (5)	215 (16)	190 (23)	491 (36)	804 (58)
TCA (N = 709)										
No	378 (94)	542 (76)	204 (67)	369 (52)	247 (35)	387 (96)	582 (82)	227 (74)	401 (57)	265 (37)
Yes	26 (6)	167 (24)	102 (33)	340 (48)	462 (65)	17 (4)	127 (18)	79 (26)	308 (43)	444 (63)
Other[e] (N = 237)										
No	151 (92)	201 (85)	49 (75)	138 (58)	92 (39)	156 (95)	212 (89)	53 (82)	147 (62)	97 (41)
Yes	13 (8)	36 (15)	16 (25)	99 (42)	145 (61)	8 (5)	25 (11)	12 (18)	90 (38)	140 (59)
	Remitters					Stable Remitters				
Treatment, N (%)	Week 1	Week 2	Week 3[b]	Week 4	Beyond Week 4	Week 1	Week 2	Week 3[b]	Week 4	Beyond Week 4
Placebo (N = 641)										
No	547 (97)	597 (93)	501 (89)	533 (83)	460 (72)	561 (99)	621 (97)	529 (94)	562 (88)	490 (77)
Yes	17 (3)	43 (7)	63 (11)	107 (17)	180 (28)	3 (1)	19 (3)	35 (6)	78 (12)	150 (23)
Mirtazapine (N = 3406)										
No	2568 (97)	3048 (90)	1536 (82)	2572 (76)	2072 (61)	2609 (98)	3165 (93)	1649 (88)	2722 (80)	2141 (63)
Yes	87 (3)	349 (10)	342 (18)	825 (24)	1325 (39)	46 (2)	232 (7)	229 (12)	675 (20)	1256 (37)
Mirtazapine (rapid titration, N = 202)										
No	194 (96)	175 (87)	100 (80)	151 (75)	132 (65)	196 (97)	182 (90)	107 (86)	159 (79)	135 (67)
Yes	8 (4)	27 (13)	25 (20)	51 (25)	70 (35)	6 (3)	20 (10)	18 (14)	43 (21)	67 (33)
Venlafaxine (rapid titration, N = 190)										
No	186 (98)	177 (94)	102 (89)	150 (79)	133 (70)	188 (99)	182 (96)	104 (90)	157 (83)	135 (71)
Yes	3 (2)	12 (6)	13 (11)	39 (21)	56 (30)	1 (1)	7 (4)	11 (10)	32 (17)	54 (29)
SSRI (N = 1378)										
No	1285 (98)	1273 (93)	719 (87)	1110 (81)	845 (61)	1292 (99)	1307 (95)	755 (91)	1158 (84)	866 (63)
Yes	21 (2)	102 (7)	107 (13)	265 (19)	530 (39)	14 (1)	68 (5)	71 (9)	217 (16)	509 (37)
TCA (N = 709)										
No	396 (98)	650 (92)	261 (85)	541 (76)	428 (60)	401 (99)	667 (94)	278 (91)	565 (80)	437 (62)
Yes	8 (2)	59 (8)	45 (15)	168 (24)	281 (40)	3 (1)	42 (6)	28 (9)	144 (20)	272 (38)
Other[e] (N = 237)										
No	163 (99)	229 (97)	62 (95)	200 (84)	163 (69)	164 (100)	235 (99)	63 (97)	206 (87)	166 (70)
Yes	1 (1)	8 (3)	3 (5)	37 (16)	74 (31)	0 (0)	2 (1)	2 (3)	31 (13)	71 (30)

[a]Responders were defined as having a reduction in HAM-D-17 score of ≥ 50% from baseline. Stable responders were defined as having a reduction in HAM-D-17 score of ≥ 50% from baseline at 4 weeks of treatment and at study endpoint.
[b]Remitters were defined as having a reduction in HAM-D-17 score to ≤ 7 points. Stable remitters were defined as having a reduction in HAM-D-17 score to = 7 points at week 4 of treatment and at all subsequent assessments.
[c]Percentages are based on the total number of patients actually assessed at a given study week.
[d]Week 3 was not a scheduled assessment in all studies.
[e]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

(predominantly imipramine) and monoamine oxidase inhibitors (predominantly phenelzine). These agents must be started at subtherapeutic doses and titrated upwards during the first 2 weeks of treatment to improve tolerability. Thus, the association of early improvement with placebo response in their analyses could reflect both the requirement of a more substantial level of improvement and the fact that therapeutic doses of TCAs and monoamine oxidase inhibitors were generally not achieved until the end of the first 2 weeks of therapy.[13]

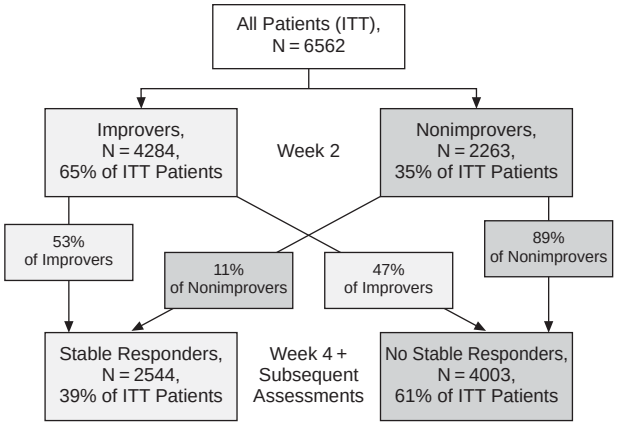
It is important to note that high sensitivity does not mean that the presence of early improvement invariably leads to stable response or remission, as indicated by the limited specificity of early improvement. In fact, the

Table 4. Predictive Value of Early Improvement[a] for the Intent-to-Treat Population

Treatment	Sensitivity (95% CI)[b]	Specificity (95% CI)[b]	Positive Predictive Value (95% CI)[b]	Negative Predictive Value (95% CI)[b]	False-Positive Rate (95% CI)[b]	False-Negative Rate (95% CI)[b]
Stable Responder Rates						
Placebo (N = 640)	88 (82 to 93)	60 (56 to 93)	43 (38 to 49)	94 (91 to 96)	40 (35 to 44)	12 (7 to 18)
Mirtazapine (N = 3397)	91 (89 to 93)	48 (46 to 51)	56 (54 to 58)	88 (86 to 90)	52 (49 to 54)	9 (8 to 11)
Mirtazapine (rapid titration N = 202)	98 (93 to 100)	43 (33 to 53)	60 (52 to 68)	96 (86 to 100)	57 (48 to 67)	2 (0.3 to 8)
Venlafaxine (rapid titration, N = 189)	96 (89 to 99)	45 (35 to 54)	56 (47 to 64)	94 (84 to 99)	56 (46 to 65)	4 (1 to 11)
SSRI (N = 1375)	88 (85 to 91)	50 (47 to 54)	50 (46 to 53)	86 (85 to 91)	50 (46 to 53)	12 (9 to 15)
TCA (N = 709)	89 (85 to 92)	46 (41 to 51)	56 (51 to 60)	84 (79 to 89)	54 (49 to 59)	11 (8 to 15)
Other (N = 237)[c]	81 (72 to 89)	53 (45 to 61)	51 (43 to 60)	82 (73 to 89)	47 (39 to 55)	19 (11 to 29)
Stable Remitter Rates						
Placebo (N = 640)	91 (82 to 96)	53 (49 to 57)	21 (17 to 26)	98 (95 to 99)	47 (43 to 51)	9 (4 to 18)
Mirtazapine (N = 3397)	93 (91 to 95)	38 (36 to 40)	27 (25 to 29)	96 (94 to 97)	62 (60 to 64)	7 (5 to 10)
Mirtazapine (rapid titration N = 202)	100 (92 to 100)	30 (23 to 38)	28 (21 to 36)	100 (93 to 100)	70 (62 to 77)	0 (0 to 8)
Venlafaxine (rapid titration N = 189)	100 (89 to 100)	33 (26 to 41)	23 (17 to 31)	100 (93 to 100)	67 (59 to 74)	0 (0 to 11)
SSRI (N = 1375)	90 (86 to 94)	42 (39 to 45)	23 (20 to 25)	96 (94 to 97)	58 (56 to 61)	10 (6 to 14)
TCA (N = 709)	92 (86 to 96)	37 (33 to 41)	27 (23 to 31)	95 (91 to 97)	63 (59 to 67)	8 (4 to 14)
Other (N = 237)[c]	87 (70 to 96)	44 (37 to 51)	19 (13 to 26)	96 (90 to 99)	56 (49 to 63)	13 (4 to 30)

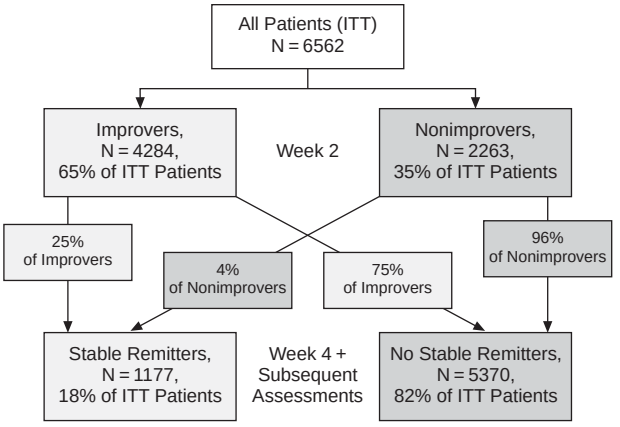
[a]Early improvement was defined as having a ≥ 20% reduction of HAM-D-17 total score within the first 2 weeks of antidepressant therapy.
[b]Fischer exact CI.
[c]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 2. Patient Flow for Stable Responders[a]



[a]The number and percentage of patients who became stable responders were determined from patients who improved with treatment at week 2 and from those who initially did not improve but did so at week 4 and at the end of treatment. All treatments, including placebo, are represented.
Abbreviation: ITT = intent-to-treat.

Figure 3. Patient Flow for Stable Remitters[a]



[a]The number and percentage of patients who became stable remitters were determined from patients who improved with treatment at week 2 and from those who initially did not improve but did so at week 4 and at the end of treatment. All treatments, including placebo, are represented.
Abbreviation: ITT = intent-to-treat.

consistently higher negative predictive values in relation to the positive predictive values indicate that the absence of early improvement is more predictive of a later lack of stable response or stable remission with continued treatment. Early improvement was a clinical predictor of treatment success in roughly 50% of early improvers. However, unsuccessful treatment outcome was predicted for roughly 90% of those who did not experience early treatment improvement.

In further regard to the predictive value of a lack of early improvement, it should be noted that it is unclear whether these results would change if the treatment duration were extended. The possibility that some portion of week 2 nonimprovers may have demonstrated sustained response or remission if treatment was extended should be acknowledged. However, based on our analyses, we would argue that the number of patients doing so would be small. Furthermore, the overall response and remission rates reported in this analysis (51%–63% and 29%–37%, respectively) are comparable to those of other published reports, including the first step of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

study,[28] which reported a 48.6% response rate at 5.5 weeks and a 36.8% remission rate at 6.3 weeks. This outcome suggests that any further additional improvement in the treatment groups would probably be minimal. It should also be noted that, because the current analysis primarily included patients with acute MDD, it is unclear how the predictive indices might change in patients with chronic depression or a complicated treatment course.

It is also important to note that our contention that early improvement is a critical factor that can be used to predict treatment response still implies that in a majority of patients, full treatment benefit will require continued treatment of several weeks. Clearly, substantial additional improvement in depressive symptoms can be observed after treatment periods exceeding 8 weeks.[1,2,29–31] This notion is again supported by the results from the STAR*D trial.[29] Furthermore, a meta-analysis published by Taylor et al.[2] concluded that improvement in depressive symptoms can be observed after 1 week of treatment, but improvement continues for at least 6 weeks after treatment initiation. Our data would suggest that improvement, or the lack thereof, that is observed at later time points can be predicted by improvement under treatment at week 2. That is, most individuals meeting criteria for response or remission at later time points would demonstrate some evidence of improvement, even if full response or remission is not attained, at week 2.

Treatment regimen can be a mitigating factor that influences the onset of antidepressant action. In fact, response to many agents,[31,32] but not all,[33,34] is facilitated by dose escalation in previously nonresponsive patients. Bernardo et al.[32] reported that fast titration with venlafaxine produced more rapid improvement in depressive symptoms than did slow titration, a finding that is consistent with results of the present analysis. In addition, rapid mirtazapine dose titration during the first week of treatment enhanced all indices of predictive value. It should be noted that the effectiveness of dose escalation is not limited to the early treatment period. Heiligenstein et al.[31] reported that dose escalation of the SSRI fluoxetine improved depressive symptoms at treatment week 10 in more than two thirds of patients who had not responded at week 4.

The high negative predictive value and low false-negative rates we observed indicate that the absence of early improvement should prompt clinicians to consider changing the treatment regimen after 2 weeks of treatment, because nonimprovers at week 2 are unlikely to benefit from their current treatment. Early identification of potential treatment failures could help alter the treatment management approach to one with a higher likelihood of success. It is hoped that early monitoring and modification of depression therapy will reduce patient distress, resource utilization, medication noncompliance, and risk of suicide.

Monitoring of early improvement as a predictor of treatment outcome is of further clinical value because it can be easily implemented in the clinical setting. It does not require an expensive technical investment and can be applied worldwide. Implementation requires only an assessment of depression severity at baseline and at weekly intervals with an adequate scale. In our experience, the choice of the HAM-D-17 or MADRS scale did not significantly influence the results, which argues in favor of the robustness of early improvement as a predictor of later clinical outcome. Given the potential for saving time and costs by using early improvement as a predictor of later outcome, a weekly investment of 20 to 30 minutes for the rating of depressive symptoms in the clinical setting seems reasonable.

On the basis of the findings from this analysis of predominantly 6-week clinical trials, we recommend the following clinical guidelines for antidepressant therapy: (1) before starting treatment, a baseline assessment of the severity of depressive symptoms should be performed using a validated scale, such as the HAM-D-17, MADRS, Quick Inventory of Depressive Symptomatology–Self-Report, or 9-item Patient Health Questionnaire; (2) assessments should be made on a weekly basis to monitor changes in depressive symptoms during the course of treatment; and (3) antidepressant medications should be titrated rapidly within the first week, if possible, until therapeutic response is seen or the highest tolerated dose is achieved. It should be noted that it is unclear if the results of this analysis and the treatment guidelines outlined above can be generalized to longer duration trials. However, in the context of 4- to 6-week trials, using such a strategy to identify patients with early improvement would indicate that the treatment strategy should be continued without adaptation and monitored for continued efficacy; subsequent response or remission at 4 to 8 weeks can be expected in a large percentage of patients. If early improvement is not observed within the first 2 weeks of therapy, there is a substantially smaller chance of stable response or remission, and individual treatment adaptations should be made as early as possible and can be tailored to the patient's needs.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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