# Clinical Significance of Monitoring Early Symptom Change to Predict Outcome

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Even with efforts to develop medication algorithms for the treatment of psychiatric illnesses, there is no single authoritative method that can be used to incorporate multiple factors in the treatment decision process. For this reason, physicians are faced with the often daunting task of sifting through the numerous treatment options for psychiatric illness to develop an approach that will prove the most successful for their patients. Investigating patient patterns of response, particularly during the acute phase of treatment, and bearing them in mind when developing treatment protocols may assist clinicians in optimally managing the degree and course of symptom response. We present here a consideration of the timing and nature of response as well as individual patient predictors, which may impact therapy decisions. Furthermore, we explore the clinical significance of integrating response patterns into the treatment approach. We believe that an analysis of response patterns, in conjunction with the use of other practice guidelines, is a viable method to more effectively navigate critical decision points in the treatment process and ultimately have a dramatic effect on patient outcome.

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Treatment research to date often has focused on the question of what leads to medication efficacy in most patients. As a result, there have been various efforts to establish a hierarchy of effectiveness among pharmacologic agents or particular strategies. These efforts have led to the development and evaluation of treatment algorithms, such as the Texas Medication Algorithm Project (TMAP).[1,2] Less emphasis has been placed on other interventions, such as utilization of critical decision points based on patient-specific, outcome-based variables that may inform clinicians if and when changes to a selected treatment plan should be pursued. As a supplement to efficacy studies, researchers must examine methods to assess other factors that can aid physicians in making the most appropriate decisions in aspects of clinical management.

Remission (the virtual absence of symptoms), as opposed to mere response, must be the principal criterion in the determination of the most effective treatments. Achieving complete recovery, as measured by symptom improvement and restoration of functioning, should be the expected, rather than the optimal, goal of treatment. How best to achieve symptomatic remission is only the first consideration in defining a successful intervention; initial treatment response does not guarantee symptom remission. Interestingly, 20% to 30% of treatment responders fail to achieve remission (M.H.T., A. J. Rush, M.D., unpublished manuscript, 2000). We intend to investigate patterns of response during acute-phase treatment with antidepressants for major depressive disorder in order to arrive at conclusions that may inform clinicians if and when modifications to a treatment plan should be made to ensure full recovery.

Pharmacotherapy options for psychiatric illnesses are ever increasing, not only owing to development of new drugs but also as a consequence of emerging novel treatment strategies in the use of both long-available and newly available agents. Physicians are faced with the challenge of incorporating these options into treatment approaches based on specific patient needs, taking into account several factors. A primary factor is the trajectory of response during the acute phase of treatment. This facet includes knowledge of prior medication trials as well as of any current psychotropic medication use. Interpretation of such information, especially in the case of partial or nonresponse to a medication, may be complicated. Methods to determine the most appropriate clinical recommendations for patients based on the initial treatment response lack systematic evaluation. Recently, research using medication algorithms has been initiated, in part to address this deficiency. However, no one method, including use of

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Table 1. Classification of Patients' Response as Assessed by Symptom Improvement

| Response Category | Level of Improvement |
|---|---|
| Nonresponse | < 25% |
| Minimal response | ≥ 25% but < 50% |
| Response | ≥ 50% but < 75%[a] |
| Remission | 75% to 100% |

[a]Traditional definition of *response* in majority of randomized controlled trials is 50% or greater reduction in symptoms as measured on rating scales (e.g., the Hamilton Rating Scale for Depression).

algorithms, has been shown to be sufficient to provide ultimate authority for such decisions. We believe that an examination of predictable response patterns in symptom improvement over the first few weeks of treatment, used together with other practice guidelines, may assist clinicians in optimally managing the degree and course of symptom response.

## DEFINING RESPONSE

Various criteria have been used to define the extent of response, based on evaluations of symptom severity at a given point in treatment compared with baseline. Degrees of response can be categorized according to the percent reduction in symptoms at a given week of treatment (Table 1). For depression, symptoms are usually assessed by the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[3,4] although other assessment instruments also have been used. In addition to comparing percent changes from baseline, treatment response may be assessed by setting an absolute criterion score.

Degree of response can be influenced by a number of external factors, such as situational or environmental conditions, the quality of interaction/therapeutic alliance with the clinician, a placebo effect, or even spontaneous remission. Response is usually progressive, with improvements occurring incrementally over the first few weeks. Some studies also have reported that a significant number of patients who have achieved response or remission continue to improve several weeks into their treatment.

### Remission

Remission is achieved when symptom reduction from baseline is at least 75%. Most of the relevant literature has dealt with symptomatic response (defined below) as opposed to remission. However, as mentioned previously, the focus of this article is the application of techniques to achieve patient remission. We will provide a more comprehensive definition of *remission* later in this article.

### Response

Most randomized controlled trials use the definition of ≥ 50% improvement in symptom severity from baseline on the HAM-D as a criterion for response. When assessing symptoms using an absolute score, a HAM-D-17 score of ≤ 10 often is used,[5,6] although maximum HAM-D-17 scores ranging from 10 to 12 have also been used to represent patients exhibiting this degree of response. Patients who exhibit significant but incomplete response may represent the greatest challenge to clinicians, since treatment changes can undermine, as well as augment, existing improvements.

### Minimal Response

A 25% to 49% reduction in HAM-D indicates a minimal response. For this category of symptom response, criterion scores are less informative than percent reduction and therefore are generally not utilized in classifying minimal response.

### Nonresponse

Less than a 25% reduction in symptoms signifies trivial improvement and in essence indicates nonresponse. For obvious reasons, generic criterion scores are not applicable in the case of nonresponding patients.

## DEFINING ADEQUATE DURATION OF TREATMENT TRIAL

There is some controversy as to when nonresponse to treatment should be declared. Should the cutoff date be 8 weeks, 10 weeks, or 12 weeks from baseline? According to some sources, the wait should be even longer. Ten to 12 weeks is probably the maximum length of time that patients will endure a nonefficacious treatment. We consider a patient a nonresponder if his or her symptoms have improved less than 25% with an adequate dose of medication. The TMAP protocol recommends dose escalations at weeks 4, 6, 8, and 10 to ensure optimal outcome and considers a 10- to 12-week trial adequate in most cases for patients with major depressive disorder. Our recommendations are consistent with the TMAP criteria, although we do acknowledge that there may be certain conditions in which treatment for a given patient for a shorter duration (e.g., 6 weeks) at a recommended adequate dose of medication may be sufficient to declare nonresponse. We believe that this article will bring more accuracy and uniformity to guideline recommendations regarding physician management of treatment duration.

## TIMING AND NATURE OF RESPONSE

Are there really differences between early responders and late responders? When can we identify these differences to guide treatment? If we can predict these groups at the outset, we can at least help patients understand that they are likely to fall into one group as opposed to another, and that may improve compliance and the long-term therapeutic alliance.

### Early Versus Late Response

Patients exhibiting a 50% or greater decrease in their HAM-D scores on or before week 4 are considered early responders. Failure to achieve that decrease in HAM-D score until after week 4 constitutes a late response.

### Sustained Response

Another way to characterize treatment response is whether or not it is sustained. *Sustained response* is defined as 2 consecutive weeks of improvement in symptoms that meets the response criterion. This designation of *sustained* often translates into a drug response being considered authentic. A prolonged period (i.e., 2 months) of sustained remission indicates full remission of the disorder, according to DSM-IV.[7] Reemergence of depressive symptoms following the 2-month symptom-free period can be seen as recurrence.

Quitkin et al.[8] and Stewart et al.[9] describe response patterns as early or delayed and either persistent or nonpersistent. (Quitkin et al.[8] have argued that a true medication effect is likely to be delayed but persistent, as opposed to an early nonpersistent response that, according to the authors, is indicative of a placebo effect.) In one study,[8] the pattern of response for patients who were assigned placebo was compared with that of patients who received active drug. A delayed and persistent improvement differentiated patients who showed a response to antidepressant medication from those who showed an early or nonpersistent benefit, which characterized a placebo response. From these observations, Stewart et al.[9] predicted, and then confirmed, that patients with a true drug response are most likely to experience a sustained benefit if they continue to receive the drug. The authors also concluded that patients with a placebo response would have a nonpersistent response. Although their findings do not explain the early persistent medication responders, the theoretical position is compatible with the approach we present here. Methodologically, such analyses warrant further investigation.

## PREDICTORS OF RESPONSE

### Baseline Predictors of Response

Physicians must choose a pharmacologic intervention predicated on whether, in their judgment, it will be tolerable and effective for a patient. Much research is designed to determine the probability that a particular agent will be effective for a particular patient or patient population. Usually the intervention is assessed in terms of how effective an agent is for a particular disorder based on group data, as in a clinical trial. Another method involves looking at variables that may identify physiologic, demographic, or disease characteristic parameters for specific drugs.[10]

Numerous variables have been evaluated for their utility as general prognostic indicators of outcome and/or their predictive capability with respect to a specific drug or treatment strategy. Variables likely to aid physician decisions are diverse: physiologic attributes, demographic characteristics, temperament, course of illness descriptors, symptom subtypes/clusters, symptom patterns, and genetic factors.[10,11]

The single most reliable variable for predicting treatment outcome is baseline symptom severity.[12] The less sick a patient is when presenting for treatment, the better the outcome is likely to be. Tedlow et al.[12] found that baseline severity of depression and anxiety was associated with the probability of response, with lower levels of severity being significantly correlated with greater improvement as assessed by change in Clinical Global Impressions scale[13] or HAM-D scores. Other studies have found that patients presenting with significant comorbid anxiety symptoms have a poorer response to antidepressant therapy. Fava et al.[14] found that nonanxious depressed patients (patients without any comorbid anxiety disorder) improved slightly but significantly more during treatment than patients with anxious depression on all outcome measures when treated with fluoxetine.

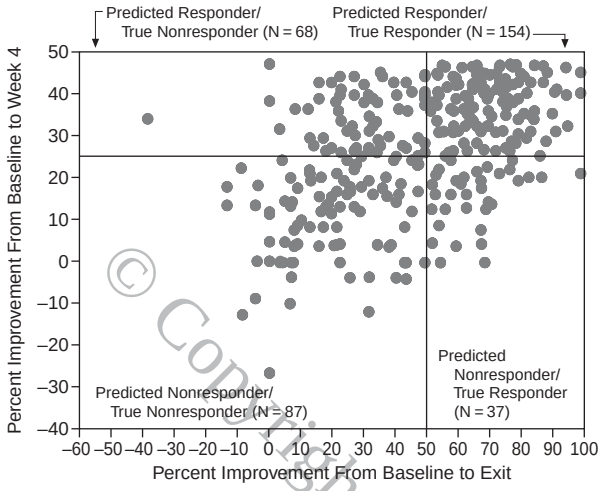
Each of these approaches to predicting outcome has limits to its effectiveness. Therefore, additional methods must be sought. We believe prediction of patient symptom response upon initiation of treatment can be used in conjunction with the methods just described to optimally guide physicians' decisions.

### What Is the Value of Evaluating the Trajectory of Early Symptom Response After Treatment Initiation?

The rationale for developing methods or tools to assist physicians in making optimal treatment decisions is clear. Both patients and physicians benefit economically in terms of cost savings and in terms of wellness or quality of life.

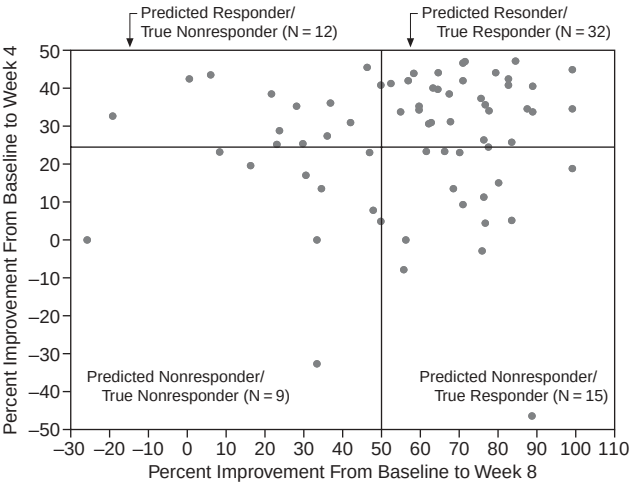
When do you decide to continue with a particular treatment? When do you increase the dose of a medication? These questions hinge on whether a patient is an early responder, late responder, or nonresponder. Therefore, a means to predict membership in these groups would be useful. Physicians, as well as patients, may benefit tremendously from this information. Reducing the number of weeks a patient takes medication that is likely to remain ineffective may produce an improvement in terms of cost, function, and overall reduction in symptom impairment. Patients are impatient for recovery, but so are physicians. Looking at survey data, faced with an incomplete response at the end of 4 weeks, physicians often begin saying, "We should make some changes." Results from various database analyses indicate that it may not be wise to start changing treatment tactics at the end of 4 weeks, even if there is not a profound improvement. By looking at patterns of response, we hope to elucidate criteria that can reliably aid this aspect of decision making.

Figure 1. Nefazodone Treatment of Depressed Patients[a]




[a]Data from Feiger et al.[15] Scatter plot shows the distribution of predicted versus true responders and nonresponders based on percent improvement from baseline (N = 346).

Figure 2. Citalopram Treatment of Depressed Patients[a]




[a]Data from Robert and Montgomery.[17] Scatter plot shows the distribution of predicted versus true responders and nonresponders based on percent improvement from baseline (N = 68).



## CRITICAL DECISION POINTS

### What Is the Clinical Significance of Critical Decision Points?

Critical decision points are designed to prompt an assessment of symptoms and a determination of the need for change in strategy or tactics. At each critical decision point, the physician should assess the patient for improvement and make a decision either to continue or to change treatment based on improvement in symptoms.

Ensuring an adequate treatment trial of at least 4 to 8 weeks at the recommended dose range enhances response to a medication. However, if a patient fails to respond to an adequate dose of a specific medication for 4 to 6 weeks or has an unsatisfactory or partial response by weeks 6 to 8, an alternative treatment plan is recommended. The duration of a treatment trial may be extended to 8 to 12 weeks if an augmentation strategy has been instituted in patients with a partial response. Application of response pattern criteria for patients at critical decision points could reduce the likelihood that a nonresponding patient would be continued on an ineffective treatment or that a late responder would have treatment terminated.

### Predicting Response on the Basis of Postbaseline Symptom Change

Although differentiating early-responding patients from those who respond late or not at all may be of value to basic research into the etiology of depression, the usefulness of accurately describing a response pattern is only capitalized on if it is truly predictive. In other words, it must be evident before patient response is declared, not in retrospect. If at 4 weeks the predictive value of a variable is only slightly better than at 5 weeks, then it obviously has much less utility than a variable that has a high positive predictive value at week 2 or 3.

To investigate the predictive power of applying response pattern criteria at critical decision points, we retrospectively analyzed data from a subset of 993 patients with nonpsychotic major depression after 12 weeks of acute phase treatment with nefazodone.[15] In contrast to a previous study by Nierenberg et al.,[16] we have chosen to exclude data for early responders in order to look exclusively at the subgroup of patients for whom we are trying to predict response. Part of our rationale for excluding early responders is that there may be inherent differences between patients who respond early and patients who respond late. Such differences would confound the generalizability of our findings.

The data presented here were taken from a larger multicenter, double-blind, randomized continuation phase trial.[15] As shown in Figure 1, at week 4, 154 patients (44.5%) were correctly identified as nefazodone responders and 87 patients (25.1%) as nonresponders. The risk of incorrectly identifying a patient as a responder was 19.6% (N = 68); the risk of incorrectly identifying a nefazodone nonresponder was 10.7% (N = 37).

Similarly, Figure 2 shows response patterns of patients after 4 weeks of treatment with citalopram. The data were taken from a depression relapse study in which patients with major depressive disorder entered an 8-week period of open treatment with citalopram.[17] At week 4, 32 patients (47.1%) were correctly identified as citalopram responders and 9 patients (13.2%) as nonresponders. The risk of incorrectly identifying a patient as a responder was 17.6% (N = 12); the risk of incorrectly identifying a citalopram nonresponder was 22.1% (N = 15).

One weakness of these preliminary analyses is that the medications used often require a dose titration to provide adequate treatment. This leads to the question of whether an artificial late response is observed in some patients. A study designed to resolve this concern would evaluate the response pattern of patients who were randomly assigned either to continue the current dose or to have a dose increase at a specified week early on in treatment based on symptom severity.

Baseline response rates to antidepressant treatment have a significant impact on the predictive value of the model we present. The higher the baseline rate, the smaller the degree of prognostic power. Because of this inherent statistical artifact, determining baseline rates for patients according to categories of response, e.g., nonresponders or late responders, and eliminating patients who are early responders provides opportunity for elucidation of patterns that may be clinically meaningful.

Further analyses of response patterns in placebo versus drug responders should also be informative. Few studies have made such comparisons, and those that exist have been criticized for methodological shortcomings. Reported nonresponse rates are biased in that they overestimate true nonresponse rates owing to premature patient dropout.

There is an additional intrinsic flaw in the data used in this method of evaluation. Not knowing the true outcome of nonresponders who do not complete the study reduces the precision of characterizing categorical baseline rates of response. The analyses presented here reiterate the importance of adequate duration of treatment in eliciting response.

Distinguishing late responders from nonresponders is important because it determines how long to continue treatment. If a patient is an early responder, there is clear improvement by week 2, and the goal is to maintain him or her on treatment with the medication until full remission. But if there is no change in the first 2 or 3 weeks, how can we distinguish the late responder from the nonresponder?

Preferred use of a more sensitive cutoff versus a more specific one depends on the history of the patient treated. General findings from group data can instruct a clinician for a specific patient, and the criteria can be adapted to these needs. Intuitively, if a patient has tried multiple medications, clinicians should be inclined to base their decision on a less specific, and thus more sensitive, criterion for response. However instinctive this would seem, the data suggest that clinicians' decisions routinely do not conform to this judgment.

Development of a method to differentiate late responders from nonresponders could have significant clinical utility, especially in cases of patients who have failed multiple medication trials. If a monotherapy has a relatively high chance of being effective, continuation of the medication would be preferable to beginning augmentation or combination therapy or to switching medications.

### Can We Distinguish Between Late and Nonresponders on the Basis of Patterns of Early Symptom Change?

In predicting patient response, our approach to these analyses has the potential to err either by classifying a patient who is a true nonresponder as a responder (a type I error) or, conversely, by identifying a patient who truly responds to treatment as a nonresponder (a type II error). The potential for each type of error can be reduced by setting parameters for response but not without a counteracting effect in the opposite direction. Therefore, the ramifications for each type of error should be considered when determining a response criterion based on symptom rating scale scores. A more sensitive criterion would increase the likelihood of a type I error being made. Practically speaking, this would mean that an ineffective treatment would be continued because of a less stringent HAM-D score being set for response. Alternatively, a more specific criterion for response could result in a type II error, since requirement of a lower HAM-D score could falsely result in the termination of treatment for patients who would eventually respond. The clinical impact of these 2 types of errors must be carefully weighed when applying this methodology to an individual patient. We hope to minimize either of these occurrences through careful interpretation and appropriate application of symptom response pattern findings.

## DEFINING REMISSION

Clinically, remission can be used as a benchmark when evaluating the current degree of symptoms (symptomatic remission) or the state of the depressive episode (episodic remission). Symptomatic remission can be measured using a criterion of a HAM-D total score of $\leq 7$. Episodic remission as defined by DSM-IV[7] is the abating of symptoms and a restoration of function for an extended period of time (2 months) after a patient has achieved sustained, full response to treatment.

According to the DSM-IV,[7] episodic remission can be further differentiated as either full or partial. Partial remission may indicate that the patient has achieved remission of symptoms for a period of time falling short of 2 months or that the patient is continuing to experience residual symptoms following a depressive episode. Cornwall and Scott[18] reported that up to one third of subjects treated for depression achieve only a partial remission. Patients who achieve partial remission between episodes of depression are said to exhibit poor interepisode recovery. These patients are at a greater risk for recurrence of symptoms that may lead to relapse or, if prolonged, the onset of another depressive episode.

There is a small group of patients who have symptom response but no remission. These patients may require a different strategy, such as introducing an augmenting agent. This group is most likely to benefit from consideration of a change in treatment. However, prevalence rates

for patients who achieve symptom response but not symptom remission must be viewed cautiously since there is a lack of data available for late responders in most studies. Analysis of response patterns over longer study periods would provide a more accurate evaluation.

### Lag Between Response and Remission

There is some exciting information about the lag between symptom response and symptom remission and what percentage of patients eventually do achieve remission. The likelihood of remission is high for patients who respond to a medication. An examination of individual patient outcomes may provide information regarding the number of weeks it takes for a patient to get to remission after exhibiting a response.

### Predictors of Relapse or Recurrence

Relapse and recurrence are differentiated by the timing of symptom presentation in the course of a depressive illness. A patient is considered to have relapsed if he or she experiences a return of symptoms before full remission (2 months without symptoms) has been achieved. A recurrence, however, identifies the onset of a new depressive episode after full remission has been achieved.

Success of an intervention must be weighed against the overall course of the depressive illness. This is often overlooked by clinicians, who may fail to implement or follow a plan for maintaining the initial response. Lavori et al.[19] reported that 13% of responding patients will have a recurrence of symptoms within 6 months. The cumulative probability of a recurrence increases with time. The probability rate doubles at 1 year and triples at 2 years. At 5 years, the rate of recurrence is an incredible 75%.[20]

Clinicians often maintain a restricted view of overall outcomes in regard to patient functioning. There has been a strong tendency to evaluate wellness based solely on symptom improvement.

### Nature of Interventions for Partial Responders

Studies have shown that among partial responders to serotonin reuptake inhibitors, patients demonstrate a higher recovery rate with augmented antidepressant therapy compared with antidepressant treatment alone. Various pharmacologic strategies have been developed to treat such cases, including augmentation of therapy with drugs such as liothyronine sodium, lithium, and buspirone. These augmentation strategies have clearly illustrated improved efficacy and clinical utility, possibly resulting in complete or near-complete recovery in up to 60% of cases.[21]

Treatment-resistant depression is defined as depression that is resistant to 2 courses of monotherapy with pharmacologically different antidepressants given in an adequate dose for a sufficient length of time. It is estimated that about 20% of depressed patients are resistant to monotherapy. If a patient has not attained complete remission of symptoms after adequate trials of medication treatment, then it may be necessary to accept incomplete recovery (25%–75% symptom reduction) as a satisfactory outcome. The duration of critical decision points may need to be extended in order to allow slow responders a longer period of time to show improvement with their medication.

## CONCLUSIONS

Analysis of response patterns may be a viable method with which to develop criteria that can be used in determining critical decision points. The potential for this intervention to have a dramatic impact on patient outcomes, if incorporated with other treatment planning guidelines, is the impetus for our inquiry. Future studies specifically designed to incorporate assessment of patient outcome data using the method we have presented should lead to improved predictive reliability and validity of this approach. Future investigations will also be required in determining and implementing appropriate incorporation into clinical practice.

*Drug names:* buspirone (BuSpar), citalopram (Celexa), fluoxetine (Prozac), liothyronine (Cytomel, Triostat, and others), nefazodone (Serzone).

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