Conceptualization and Rationale for Consensus Definitions of Terms in Major Depressive Disorder

Remission, Recovery, Relapse, and Recurrence

Ellen Frank, PhD; Robert F. Prien, PhD; Robin B. Jarrett, PhD; Martin B. Keller, MD; David J. Kupfer, MD; Philip W. Lavori, PhD; A. John Rush, MD; Myrna M. Weissman, PhD

• In 1988, the MacArthur Foundation Research Network on the Psychobiology of Depression convened a task force to examine the ways in which change points in the course of depressive illness had been described and the extent to which inconsistency in these descriptions might be impeding research on this disorder. We found considerable inconsistency across and even within research reports and concluded that research on depressive illness would be well served by greater consistency in the definition change points in the course of illness. We propose an internally consistent, empirically defined conceptual scheme for the terms *remission, recovery, relapse,* and *recurrence.* In addition, we propose tentative operational criteria for each term. Finally, we discuss ways to assess the usefulness of such operational criteria through reanalysis of existing data and the design and conduct of new experiments.

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As clinical researchers interested in longitudinal studies of mood disorders, we became aware of marked inconsistencies in the use of terms such as *remission, recovery, relapse,* and *recurrence.* Inconsistency in the conceptualization and definition of these terms made research findings difficult to interpret and precluded comparisons of results across studies. A coherent scheme for labeling change points in the course of illness would aid in the design, conduct, and analysis of investigations aimed at understanding cause and pathogenesis, as well as those focused on the evaluation of short- and long-term effects of treatment. Accordingly, we describe a conceptual scheme for the terms *remission, recovery, relapse,* and *recurrence* and propose internally consistent, empirically testable operational criteria for each term. Finally, we briefly discuss a few ways in which such operational criteria might be tested.

See also p. 796.

THE NATURE OF THE PROBLEM IN THE LITERATURE ON NONBIPOLAR MAJOR DEPRESSION

In reviewing recent studies in nonbipolar major depression (see the accompanying article by Prien et al[1]), we found no consensus about defining change points in the course of depressive disorder. Furthermore, conceptual confusion is rampant, so that one investigator's *relapse* is another's *recurrence.* For some, *remission* and *recovery* refer to unique concepts, while others use these terms interchangeably. Many additional terms are used to refer to concepts similar to *remission, recovery, relapse,* and *recurrence.*

Consistent conceptualization and empiric validation of these terms are desirable for the following reasons: (1) improved design, interpretation, and comparison of studies of natural course and clinical therapeutic trials; (2) clarification of the relationships between biologic and psychological correlates of illness; (3) more rational drug development planning by individual investigators and the pharmaceutical industry; (4) improved guidelines for evaluation of clinical efficacy of drugs and other treatments by regulatory agencies; (5) empirically based revision of diagnostic criteria; and (6) development of improved treatment guidelines for clinical practice.

PROPOSALS FOR DEFINITIONS AND OPERATIONAL CRITERIA

The noted inconsistencies led us to consider abandoning all descriptive terms for the course of depressive illness in favor of an entirely new terminology. Ultimately, however, this might add to the current confusion. To "rescue" the terms *response, remission, recovery, relapse,*

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From the Department of Psychiatry, University of Pittsburgh (Pa) School of Medicine, Western Psychiatric Institute and Clinic (Drs Frank and Kupfer); Division of Clinical Research, National Institute of Mental Health, Rockville, Md (Dr Prien); Department of Psychiatry and Human Behavior, Brown University, Butler Hospital, Providence, RI (Drs Keller and Lavori); Department of Psychiatry, University of Texas Health Science Center, Dallas (Drs Jarrett and Rush); and Division of Clinical-Genetic Epidemiology, College of Physicians and Surgeons, Columbia Univesity, New York, NY (Dr Weissman).

Reprint requests to Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (Dr Frank).

and *recurrence*, we propose instead to redefine them using only observed course of illness. We recognize that the *meaning* of a term such as *recovery* may vary depending on the specific context in which the resolution of symptoms occurs and on the theoretical orientation of the observer. A recovery in the context of psychopharmacologic or psychotherapeutic treatments may be understood differently from one observed in the absence of any formal intervention; however, the word *recovery* should, in our view, have an unambiguous phenomenologic meaning.

We offer our conceptualization, proposed definitions, and tentative operational criteria for the purpose of critical evaluation by clinicians and clinical researchers. In addition to critiques of the conceptual usefulness of these definitions, we hope that colleagues will provide empiric critiques based on the application of these definitions to their own or other existing data sets relevant to the longitudinal course of mood disorders.

The proposed definitions and, especially, the suggested operational criteria should be viewed as working hypotheses. Like other hypotheses, these are based on a body of substantial, but incomplete, knowledge and will require testing and modification as knowledge increases.

Principles Used to Construct the Definitional Scheme

The following principles underlie the definitions developed: (1) the definitional scheme is based on observable, measurable phenomena; (2) the initiation or withdrawal of any form of treatment may change the meaning of *remission, recovery, relapse,* and *recurrence* but not their phenomenologic expression (ie, observable events); and (3) the temporal focus of the definitional scheme is lifelong rather than episode specific.

Observable Phenomena.—If the definitional scheme is based on observable, measurable phenomena, such as symptom severity, signs, or functional status, then a patient's disease status can be measured at any point in time for each of those dimensions. Then three ranges of clinical presentation can be defined on the basis of these dimensions: *asymptomatic,* indicating that the clinical presentation is within the normal or clinically acceptable range and is consistent with absence of disorder; *fully symptomatic,* indicating full syndromal expression of the disease; and *partially symptomatic,* indicating all other clinical presentations. This initial set of proposed definitions is based exclusively on severity (number and intensity) and duration of clinical symptoms. We considered including functional impairment as well; however, its relationship to symptoms is extremely complex, and we are uncertain about how to quantify this variable in a way that is *independent* of symptom status. Until we better understand how to separate functional impairment from symptoms, how functional impairment interacts with symptoms, and whether changes in functioning actually represent epiphenomena, we elected to begin with a (perhaps oversimplified) univariate framework of operationalization.

Treatment.—Once any treatment is initiated, the subsequent "natural course" of illness is, of course, unobservable. Therefore, we base our proposed definitions on *observed* clinical course and apply them in a consistent fashion, irrespective of the presence, absence, or type of treatment. The interpretation of these terms, or the meaning they may carry, may vary as a function of treatment (eg, use of the term *recovery* in persons receiving treatment does not imply that they would be asymptomatic if treatment had never been initiated or were discontinued).

Temporal Focus.—Because we wanted to build a definitional scheme that could be applied consistently to individuals with multiple episodes over a lifetime (recurrent depression) as well as to individuals who experience only a single episode, the temporal focus is the lifetime of an individual, with no particular assumption as to the number of episodes that might occur or be observed during that lifetime.

Conceptualization and Rationale for Definitions of Remission, Recovery, Relapse, and Recurrence in Major Depressive Disorder

Our initial focus is limited to unipolar major depression without dysthymia or other Axis I or II comorbidity. This simpler case provides a relatively uncomplicated basis for defining the terms of interest. By elaboration of the basic scheme proposed here, more complex diagnostic presentations can be considered in the future.

We concluded that only five terms (six, if *response* and *partial remission* are considered separately) were required to designate the relevant change points in the course of unipolar depressive illness. We also realized that a coherent definitional scheme for these terms leads to a definition of what constitutes an "episode" of illness (and vice versa).

Two types of variation are fundamental to our definitions: (1) *severity* (number and intensity of symptoms) and (2) *duration* (of symptomatic deterioration or improvement). By this simplification we hope to isolate the part of the problem of definition that depends on the description of the number and intensity of symptoms from the part that is tied to the timing of changes in symptoms.

Episode.—*Conceptualization of Episode.*—An *episode* is a period, lasting longer than D days, during which the patient is consistently within the fully symptomatic range on a sufficient number of symptoms to meet syndromal criteria for the disorder. Syndromal criteria are defined by any of several criterion-based assessment systems, such as the Research Diagnostic Criteria (RDC) or the Diagnostic and Statistical Manual of Mental Disorders. It should be noted that some of these assessment systems specify a pattern as well as number, severity, and duration of symptoms. Any period before the patient's first episode, during which the patient is in the asymptomatic range except for short periods ($<D$ days), is said to be *disorder free.* A short ($<D$ days) period during which the patient is outside the asymptomatic range is called a *flurry.* A flurry can occur either before onset or after the resolution of an episode. An episode does not end until a patient reaches recovery (see below).

Rationale for the Conceptualization of Episode.—Both clinicians and researchers must decide when a patient is clearly ill. For the clinician, this typically triggers a decision to treat; for the researcher, this designation signals the appropriateness of including the patient in a group of individuals with the same illness.

Response and Partial Remission.—*Conceptualization of Partial Remission.*—A *partial remission* is a period during which an improvement of sufficient magnitude is observed that the individual is no longer fully symptomatic (ie, no longer meets syndromal criteria for the disorder) but continues to evidence more than minimal symptoms.

Treatment is not a requirement of the definition; partial remission can be spontaneous. A *response* can be thought of as the point at which a partial remission begins. Theoretically, a response, unlike a partial remission, *does* require treatment and, thus, implies that the cause of the change in the patient's condition is known, which may or may not be a valid assumption.

Rationale for the Conceptualization of Partial Remission.—In deciding when and how to intervene, the clinician usually chooses to intervene when the patient suffers from the disorder. If the disorder is in partial remission (either by natural course or in association with treatment), the clinician may choose to observe rather than alter the patient's regimen. If a partial remission fails to become a full remission after a reasonable period, the clinician will typically alter treatment, either by increasing the intensity of the current treatment (through a higher dose of medication or more frequent therapy sessions), adding additional treatments to the one associated with the partial remission, or switching to a new treatment. If the disorder is not being treated and partial remission fails to become a full remission after a reasonable period, the clinician will typically initiate treatment. For the researcher, the failure to proceed from partial to full remission in a naturalistic study may imply the need for placing the subject in a separate category of patients. In a treatment study with a specified treatment protocol, it may imply the need to drop the subject from the study.

Full Remission.—*Conceptualization of Full Remission.*—A *full remission* is a relatively brief ($>E$ days but $<F$ days) period during which an improvement of sufficient magnitude is observed that the individual is asymptomatic (ie, no longer meets syndromal criteria for the disorder and has no more than minimal symptoms). Again, treatment is not a requirement; full remission can be spontaneous.

Rationale for the Conceptualization of Full Remission.—A declaration of remission implies that no increase in the intensity of the treatment regimen is required. Depending on the treatment and assumptions about its mechanisms of action, a full remission might imply that a decrease in the intensity of treatment could be attempted.

Recovery.—*Conceptualization of Recovery.*—A remission that lasts for F days or longer is a *recovery*. Recovery can be spontaneous and can last for an indefinite period. The term is used to designate recovery from the episode, not from the illness per se.

Rationale for the Conceptualization of Recovery.—In a clinical setting, a declaration of recovery raises the possibility that (1) treatment can be discontinued or (2) if treatment is continued, the aim is prevention of a subsequent episode. In a research setting, it might mean that treatment efforts can now be focused on maintenance of the well state or that the subject moves into a no-treatment follow-up phase in which the focus is the extent to which treatment-associated improvement is maintained.

Relapse.—*Conceptualization of Relapse.*—*Relapse* is a return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission, but before recovery as defined above. Relapse can represent a change from either partial or full remission to full syndrome criteria for the disorder.

Rationale for the Conceptualization of Relapse.—A relapse signals a need for treatment intervention or modification of ongoing treatment, since the disorder has returned. In a study of acute or continuation treatment, it may represent one outcome of interest.

Implicit in the distinction between a relapse and a recurrence (see below) is the hypothesis that relapse represents the return of the symptoms of a still ongoing but symptomatically suppressed episode, while a recurrence represents an entirely new episode; however, in a definitional scheme based exclusively on observable events, this distinction must be made in probabilistic terms.

Recurrence.—*Conceptualization of Recurrence.*—*Recurrence* is the appearance of a new episode of major depressive disorder and, thus, can occur only during a recovery.

Rationale for the Conceptualization of Recurrence.—A recurrence implies (1) the need for treatment and (2) a revision in the history of the course of illness (ie, a new episode has occurred). The latter may have prognostic and treatment implications. In studies of maintenance therapy, recurrence is typically the outcome of primary interest.

Proposed Operational Criteria

Currently there is little *empiric* justification for any set of duration measures; however, the conceptualization and rationales described above lead to a variety of testable systems. Three examples of such systems are listed in the Table and might constitute candidates for initial validation testing. All the examples, not simply the one that employs the Schedule for Affective Disorders and Schizophrenia,[2] assume a previous judgment resulting from a criterion-based assessment that the individual is in an episode. For the system based on the Schedule for Affective Disorders and Schizophrenia, we have included the durations specified in the RDC; however, we believe that the "recovery" duration is probably too short and have, therefore, specified longer durations in the other two system examples. It should not be inferred that we believe there is something inherent in the Hamilton Rating Scale for Depression[3] requiring 6 months for a recovery or in the Beck Depression Inventory[4] requiring 4 months. What we do assume is that different measures (and different severity criteria on the same measure) may lead to different duration criteria.

A wide variety of other testable systems are possible, based on measures such as the Psychiatric Status Rating,[5] the Clinical Global Impression Scale,[6] or the Inventory of Depressive Symptoms.[7] Each might have its own set of clinical ranges and durations.

PROPOSALS FOR TESTING THE DEFINITIONAL SCHEME

We have two immediate goals in proposing this definitional scheme. The first is to bring some conceptual clarity and consistency to the terms used to designate change points in the course of mood disorders. The second is to stimulate the search for empirically derived quantitative criteria to define the requirements for severity and duration in each of the criteria systems. We considered not specifying any severity or duration variables but decided that specific suggestions for these variables might aid others in evaluating the usefulness of our scheme, whether or not they agreed with the specific severity or duration variables we propose. By specifying severity and duration, we hope to stimulate others to test the validity of these systems and other systems as well.

There are several methods for arriving at empirically derived criteria to complete the scheme. One is through a review of the existing literature and a reanalysis of the data. The second is through the analysis of extant but unpublished data. The third is through the design and execution of new studies designed to obtain definitive and

specific answers to these methodologic questions. As our literature review indicates (see the accompanying article by Prien et al[1]), few published studies could serve as sources for empiric validation of this scheme. We therefore plan to begin analysis of data to which we have access and to invite others to examine their own relevant data using a common approach to analysis.

Our own approach to finding valid specifications for the severity and duration variables in our definitional scheme involves analysis of longitudinal data sets on patients in long-term treatment and follow-up studies or on patients in naturalistic follow-up studies. However, before we could begin this process, we had to establish what the criteria were for a "valid" specification variable. In brief, we had to decide what *kind* of validity was important to us.

Criteria for Validity of Severity and Duration Variables

If different versions of a definitional system, arrived at by varying one or more of the specifications, are used in statistical analyses of data, then the results can be compared on the basis of predictive power (eg, receiver operator characteristics methods[8-10]), and this predictive power can be used to examine the value of the different versions. For example, we know the RDC definitions of recovery and recurrence (at least 8 weeks well for recovery and five symptoms for recurrence) lead to a measure of "number of previous episodes" that, when used in a statistical analysis of the duration of recovery, results in considerable improvement in prediction of the hazard of recurrence (ie, the duration of recovery) over an analysis that takes no account of this variable.[11] Thus, the RDC definitions are *better* than a (trivial) definition that would compress all "episodes" into a single lump. But changing the number of weeks required for recovery from 8 to 24 would redefine "number of previous episodes" by combining RDC episodes separated by shorter durations into single episodes. This new categorization would have greater or lesser predictive power, and this would imply that it "worked" better or worse than the RDC definition. Similarly, the *outcome* of recurrence might change (in time or even in occurrence) if the RDC definition were changed. This *new* outcome might be more or less *predictable*, and the new system would cohere better or worse as a body of connected features.

Methods for Validation of Severity and Duration Variables

Each of the systems described in the Table requires a choice of severity ranges and a choice of duration requirements. The choice of severity ranges should, in general, be determined on the basis of test-retest reliability, as well as by clinical utility. That is, the *ranges* should correspond to what clinicians view as symptomatic and asymptomatic but should also be such that when the patient is in the asymptomatic range or the fully symptomatic range, the test-retest reliability during that period is high, giving reasonable stability to determinations made in the two extreme ranges. This, in turn, should yield agreement on the rest of the system, ie, remission, recovery, relapse, and recurrence.

The *durations*, on the other hand, seem to require a different type of validation. Here the criterion should be predictive validity for future course. Thus, the duration for "episode" should be set to be maximally predictive of remaining in that state. In other words, an episode is declared when it is unlikely that the patient will spontaneously recover in the next day or two. When the system has been fully tested with methods that assume a fixed set of *ranges* and variable *durations*, it may be possible to reverse the process and examine the extent to which varying the *ranges* yields better predictions.

As an example of how such validation experiments might proceed, we have focused on the concept of "recovery" and describe some validation experiments that might be undertaken.

Examples of Testable Systems of Operational Criteria

Ranges and Duration	Criterion
Schedule for Affective Disorders and Schizophrenia	
Clinical ranges	
Asymptomatic	≤2 symptoms present
Fully symptomatic	≥5 symptoms present
Durations	
Episode	≥4 wk symptomatic
Full remission	≥2 wk to <8 wk asymptomatic
Recovery	≥8 wk asymptomatic
17-Item Hamilton Rating Scale for Depression	
Clinical ranges	
Asymptomatic	Score of ≤7
Fully symptomatic	Score of ≥15
Durations	
Episode	≥2 wk fully symptomatic
Full remission	≥2 wk to <6 mo asymptomatic
Recovery	≥6 mo asymptomatic
21-Item Beck Depression Inventory	
Clinical ranges	
Asymptomatic	Score of ≤8
Fully symptomatic	Score of ≥15
Durations	
Episode	≥4 wk fully symptomatic
Full remission	≥3 wk to <4 mo asymptomatic
Recovery	≥4 mo asymptomatic

According to our conceptual scheme, the *symptom or severity level* for recovery will be identical to that for full remission. However, recovery requires the establishment of a specific *duration* criterion. One procedure for determining the most valid choice for duration might be the search for a "point of rarity," a period after which very few patients experience a return of the syndrome. The underlying assumption is that it is likely that a return of the syndrome that occurs *before* this observed point of rarity is different in some important way from one that occurs *after* it. The argument can be extended to assume that those full syndromes occurring before the point of rarity are more likely to represent reemergence of an ongoing episode (relapses), while those that occur after it are true new episodes (recurrences).

To discover whether a point of rarity exists, the rate of "failure" or syndrome return at each time point among patients still in remission at that time must be plotted. If the plot were found to have a distinct minimum between, for example, 16 and 20 weeks after remission, then there is evidence for a point of rarity and for an empiric separation between the "relapse" and "recurrence" timing. Such a point of rarity would seem to be a reasonable choice for the duration required for a remission to be considered a recovery. Here, the design of the study from which the data are drawn (eg, discontinuation vs naturalistic follow-up) is of critical importance with respect to the level of confidence in the "correctness" of the choice.

A second procedure for determining the duration required for recovery is based on the guiding principle that a remission becomes a recovery when cessation of current treatment and marginal changes in the time since the severity criteria for remission were first met no longer have any predictive leverage on the hazard of "return of full syndrome."

To test this with the use of Longitudinal Interval Follow-up Evaluation[5] data (or other more or less continuous descriptions of course), set up the time-varying Cox model or another event-history longitudinal model, with the predictors "change in treatment" and "time since start of remission" and the outcome "return of full syndrome." One expects that change downward in treatment will (on the average) be associated with increased hazard early in the period and not later. Similarly, in patients who receive no (or minimal) treatment, if the hazard stops declining after some time and levels off, one might interpret that as support for an upper limit on the time required for a remis-

sion to become a recovery (constant hazard is consistent with a memoryless process). A point of rarity is a special case of this analysis.

In naturalistic studies, one must pay attention to the determinants of treatment. The analysis of intercurrent treatment goes far beyond the scope of this communication. However, in the Collaborative Depression Study, P. W. Lavori and colleagues (M. B. Keller, MD, W. Sheftner, MD, J. Fawcett, MD, and J. Endicott, PhD, unpublished data, June 1990) found that relatively few patients continue somatic treatment beyond 6 months after remission, so that the tests of criteria of longer times may be comparatively robust. Controlled treatment trials with randomized withdrawal may provide ideal quality of evidence but may be hard to find.

Note that the principle does not rule out "fixed" predictors, such as the number of previous episodes, continuing to have predictive power. Rather, these are within-subject effects.

CONCLUSION

We have attempted to conceptualize, define, and provide tentative operational criteria for terms commonly used to characterize the course of unipolar major depression. We have enumerated the specific benefits that would result from consensus with respect to those terms.

We describe several basic principles used to construct our conceptual scheme. We offer preliminary definitions of these concepts, proposing three systems of tentative operational criteria for those variables that relate to severity and duration. We describe some of our own plans for testing these definitions and finding empirically validated numbers to attach to the severity and duration variables in the model. Finally, we enthusiastically invite others to challenge these tentative suggestions with alternate conceptualizations and for empirically derived criteria.

The proposed conceptual definitions are intended to be "atheoretical." It is hoped that these definitions will promote new studies and/or reexaminations of existing data in ways that will facilitate communication among researchers operating from different theoretical models, as well as to aid in the design and conduct of future clinical trials. Ultimately, we hope that such efforts will lead to a clearer understanding of the nature of unipolar mood disorders and, subsequently, of other mental disorders as well.

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