

Defining and Achieving Recovery From Bipolar Disorder

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Management of bipolar disorder in many ways is similar to the management of schizophrenia in that the goals in the treatment of both disorders are to avoid rehospitalization, manage behavioral symptoms, and promote functional recovery. This review will define functional recovery in bipolar disorder, discuss relapse prevention, and consider some implications for treatment. The most notable implication for treatment is that clinicians need to use stricter criteria when defining recovery in bipolar disorder. Recovery should not be defined merely by symptomatic remission or even syndromal remission; rather, recovery should include symptomatic recovery, syndromal recovery, functional recovery, and a return to an acceptable quality of life for the patient.

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In many ways, the management of bipolar disorder has features that are similar to the management of schizophrenia. That is, the management of acute episodes of mania, depression, and mixed symptomatology often shares a primary clinical goal: avoiding rehospitalizations and managing patients' behavior so that they avoid potentially serious personal consequences. Further, the long-term goal in the management of both disorders is the promotion of recovery. This article will explore the similarities in treatment between bipolar disorder and schizophrenia, elaborate on the definitions of recovery, discuss relapse prevention, and set forth some implications for treatment of bipolar disorder.

Recovery itself is a broad-spectrum goal with multiple features, each of which is required to consider the patient recovered. The concept of recovery includes achieving remission of symptomatology, functional recovery, prevention of relapse or recurrence—and in bipolar disorder, preventing both relapse of the same mood state that got the patient to clinical attention in the first place as well as switch to other mood states or developing rapid cycling—and, finally, improved subjective quality of life, all of which have to be present to consider someone recovered. This article will highlight some data from studies of both bipolar disorder and schizophrenia to describe the true convergence of all these elements of recovery in people who are receiving current treatments for bipolar disorder.

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DEFINING IMPROVEMENT IN BIPOLAR DISORDER

Defining improvement in bipolar disorder can be specified in a number of ways, but 2 concepts are syndromal recovery and symptomatic remission.¹ These are distinct from each other, and syndromal recovery is, in fact, a prerequisite for the development of complete symptomatic remission.

Syndromal Recovery

Following the definitions of Tohen et al.¹ in 2003, syndromal recovery means that the patient no longer meets the criteria for current bipolar disorder. As Tohen and colleagues defined it, that meant currently having no DSM-IV Criterion A mania items detected at a severity level greater than 3 (mild) on the Structured Clinical Interview for DSM-IV, no Criterion B items at a severity level greater than 3, and no 2 items at a level of 3 in severity. The Clinical Global Impressions Scale (CGI)² score should be 2 or less. Individuals who are recovering from mixed episodes also need to meet these requirements for the severity of their depressed symptoms as well. This means that the patient, although he or she may have some residual symptoms, no longer meets the criteria for having a mixed, manic, or major depressive episode at the time of evaluation. Tohen et al.¹ defined *syndromal remission* as sustained recovery that lasted for 8 weeks, which is admittedly a short-term criterion. This definition allows the possibility of having some residual manic or depressive symptoms, but none of the symptoms can be above mild in their severity.

Symptomatic Remission

Symptomatic remission or recovery is a criterion that is more stringent than syndromal recovery; in fact, remission criteria have been advanced recently for all serious mental

disorders, including depression, mania, and schizophrenia.^{1,3,4} Tohen et al.¹ defined *symptomatic recovery* for bipolar disorder as a Young Mania Rating Scale (YMRS) score of 5 or less and a Hamilton Rating Scale for Depression (HAM-D) score of 8 or less. Scores indicating few symptoms are relatively consistent with current conceptions of remission in unipolar depression as well. In fact, these symptoms would be seen as not being outside the normal range of experience for someone who never had a diagnosis of bipolar disorder. Symptomatic recovery is defined as a more symptom-free state than syndromal recovery.

DEFINING REMISSION IN SCHIZOPHRENIA

The prevalence and possibly the magnitude of recovery differ between bipolar disorder and schizophrenia. Explaining these differences requires exploring the meanings of recent definitions of remission in schizophrenia.

As defined by Andreasen et al.,³ remission in schizophrenia can be assessed using the Positive and Negative Syndrome Scale (PANSS), or the Brief Psychiatric Rating Scale, or the combination of the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. The PANSS, which is a 30-item 7-point rating scale, is commonly used, particularly for clinical trials. For remission of schizophrenia, all items in the criteria must have severity scores ≤ 3 (mild) for a 6-month period.

The DSM-IV does not define functional change in the remission criteria, and these remission criteria also do not address the presence of cognitive abnormalities, which may be present in people before they have ever developed psychosis.⁵ These cognitive abnormalities can be present, often unchanged in severity, in people who are no longer manifesting psychotic symptoms.⁶

FUNCTIONAL RECOVERY

Bipolar disorder is widely believed to have a better overall outcome than schizophrenia or major depression. However, prospective follow-up studies that have led to this conclusion have often focused on relapse and residual symptoms rather than on functional outcome.¹⁻³ The idea of a good treatment-related symptomatic outcome, meaning that the patient is simply less prone to relapse or has fewer residual symptoms, does not necessarily mean that the patient has experienced a functional recovery. Functional recovery is defined in terms of several different behavioral domains, including social, occupational, educational, and independent living.

Social functioning involves the ability to sustain and maintain interpersonal relationships, such as friendships, romantic relationships, and acquaintanceships. Occupational and educational functioning involves the ability

to sustain some type of productive work or activities, whether it means going to school, working at a job, or for individuals with more disability, at least participating in some type of rehabilitation program where they are being active. Independent living is a truly substantial indicator of functional recovery, especially when defined as living in a residence that the patient is fully responsible for paying for. In serious mental illness, independent living is a goal that is rarely attained, so researchers and clinicians are interested in the extent to which patients can manifest some components of independence in their living. For example, can they function appropriately in an unsupervised residence even if they do not pay the rent? Can they perform some household tasks even if they are in a supervised residence?

The choice of reference point for functional recovery is critically important to quantify the level of the functional recovery. A return to pre-illness levels is generally a lower standard than continuing on a positive course of achievement because of the poor premorbid functioning manifested by many people with schizophrenia. In individuals who developed their illness fairly early in life, their pre-illness level of functioning may never have consisted of any independent living, i.e., they may have lived with their parents, never had a job, and may have been attending school part time or not at all. Thus, returning to pre-illness level would not necessarily mean that the patient is actually doing well; it may simply mean that the patient is not doing worse than he or she was beforehand. If the patient was already doing somewhat poorly, possibly as a function of prodromal or premorbid symptoms, returning to that poor level of functioning is not necessarily a major milestone of recovery.

RELAPSE PREVENTION

Relapse prevention is another component of the recovery model. Bipolar disorder has a complex pattern of relapse. Patients may present with manic, mixed, or depressive episodes. A history of a manic or a mixed episode does not mean that the next episode will not be purely depressive in nature. Relapse prevention is complicated by several other features of bipolar disorder, including differential response of different symptoms across treatments and the development of rapid cycling in some cases. As part of preventing relapse, clinicians need to define relapse and also try to prevent the development of rapid cycling symptomatology,⁷ which is itself associated with a relatively poor outcome.

Predictors of Relapse

What predicts relapse? Approximately 1 to 2 years after any treatment for a manic or a mixed episode, the relapse or switch rates range from 35% to 60%.¹ These rates are relatively consistent with relapse rates observed in schizo-

phrenia.⁸ Many patients relapse while they are fully compliant largely because treatments for bipolar disorder do not provide complete prophylaxis,⁷ but poor adherence is also a major determinant. Poor adherence is likely to be determined by factors such as adverse events or breakthrough symptoms. Researchers need to focus on whether there are adverse effects associated with partial compliance. Does partial compliance cause a change in the course of the illness? Is partial compliance a determinant in the development of rapid cycling, which tends to be treatment-resistant?

One group of investigators⁹ has advanced a model in schizophrenia that suggests that treatment response deteriorates over time. Prospective studies^{10,11} of people with first-episode schizophrenia have shown that the rate of nonresponse to antipsychotic treatment increases by 25% during the first 5 years of illness. What this suggests is that treatment failures, determined by poor response or non-compliance, may lead to the development of nonresponse.⁹ Functional and symptomatic deterioration may result. Is the development of rapid cycling the bipolar analog of the development of treatment-resistance to antipsychotic treatment in patients with schizophrenia? Are the determinants the same? Can failures in treatment response be prevented by encouraging full compliance and making sure that patients are getting the right dose of their medication? More research must be done to answer these questions.

SUBJECTIVE RESPONSE

Subjective response is the final component of the recovery concept. A positive subjective response is related to several important features of recovery. If patients feel better about themselves and the management of their illness, they are probably more likely to take their prescribed medication. They might also be more likely to be more personally involved overall in their treatment, and they might also take personal responsibility for the management of the illness, which is critical to recovery. In order for this approach to be successful, patients will need to have a persistent positive subjective response to treatment, which will hopefully lead them to adhere to recommended treatments, develop a better therapeutic alliance, and take more personal responsibility for the outcome of their treatment.

QUALITY OF LIFE IN PATIENTS WITH BIPOLAR DISORDER

Multiple studies¹²⁻¹⁴ have been conducted on bipolar disorder and quality of life, but many of them have substantial methodological limitations. Despite these limitations, several conclusions can be drawn from these studies. A history of psychosis in people with bipolar disorder is not associated with reduced subjective quality of life, but the presence of residual depression is a major predictor

of reductions in quality of life. There is a convergence of the presence of functional disability and reduced quality of life within individuals as well. Clinicians must determine if patients have residual depressive symptoms and are functionally impaired, then plan interventions accordingly. Since it is not clear that depression leads to objective impairments in functional outcomes, successful resolution of residual depression does not guarantee improved functional outcomes.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)⁷ has shown that the majority of patients with bipolar disorder have less cyclicity in their depression than in their manic symptomatology. Even when they are characterized as euthymic, they often have residual depressive symptomatology that, while not meeting criteria for major depression, is still substantially present. Patients who appear to have recovered from a mixed or manic episode are often left with residual depressive symptomatology, which is an important treatment target. Clinicians have been reluctant to target that depression with specific antidepressant treatments because of the risk of precipitating a switch. The treatment of bipolar depression, whether it is fully syndromal or only subsyndromal, remains an important area of treatment, which will increase medication compliance and subjective quality of life.

In order to improve quality of life, it is important to carefully monitor residual symptoms, with a focus on depression in particular, as well as mania or mixed states. Adherence to a program of treatment may affect quality of life as well as symptomatic status. Quality of life may determine whether or not a patient will disappear from treatment, which is, in fact, the modal outcome for patients with bipolar disorder.

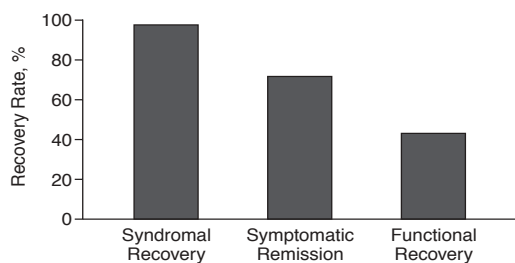
RECOVERY, REMISSION, AND RELAPSE IN MANIA VERSUS SCHIZOPHRENIA

Recovery, remission, and relapse can be compared in people with schizophrenia and people with mania using first-episode studies. Two studies^{1,4} detail the first treatment contact for large samples of people who had a manic or mixed bipolar episode¹ or schizophrenia.⁴

Tohen et al.¹ followed 166 patients for 2 to 4 years following a first episode of mixed or manic bipolar disorder. Symptomatic, syndromal, and functional recovery were measured. Functional recovery was defined as a return to pre-illness baseline, which, as stated earlier, may be viewed as a low hurdle. They also studied relapse and switch rates.

Robinson et al.⁴ followed 118 patients with a first-episode of schizophrenia or schizoaffective disorder for 5 to 6 years. Functional recovery and symptomatic remission were measured. Full recovery was defined as the concurrent presence of sustained symptomatic remission and

Figure 1. Recovery From First Manic or Mixed Episodes After 2 Years^a



^aData from Tohen et al.¹

functional recovery. Symptomatic remission was defined as being rated as mild or less on all psychosis items in the Schedule of Affective Disorders and Schizophrenia-Change Version (SADS-C) and being rated as moderate or less on all negative symptom items and sustaining these levels for 2 years. Functional performance was defined as intact social functioning and intact everyday living skills. Recovery was defined as meeting these sets of criteria. This study also looked at the rates and determinants of relapse.

Outcomes

The results of the bipolar disorder study¹ showed that, at some point in the follow-up period, about 98% of the patients met the criteria for syndromal recovery, which meant they no longer met the criteria for bipolar disorder (Figure 1). Symptomatic remission was manifested by nearly 72% of the subjects, whereas about 43% of the subjects showed functional recovery. Thus, syndromal recovery—the absence of the symptoms that are intrinsic to the definition of bipolar disorder—was twice as common as functional recovery.

In the schizophrenia study at 5-year follow-up,⁴ symptom remission for 2 years or more was seen in 47% of the subjects, functional recovery was seen in 26%, and the convergence of both functional and symptomatic recovery (i.e., full recovery for 2 years or longer) occurred in 14% of the patients. It is interesting to note that patients enrolled in this study were recovering from their first episode of illness, were involved in an active research study, and were receiving state-of-the-art treatments, yet only about 17% achieved stable, symptom-free lives that included functional recovery. This indicates that, using a slightly higher standard than the bipolar study, the rate of full recovery was particularly low.

Relapse and Switches

Rates of relapse and switch differed between the 2 studies. In the bipolar disorder study,¹ 40% of the patients experienced a direct recurrence of the same mood state as

before, and 19% experienced a switch to the other mood state. In the schizophrenia study,⁴ the relapse rate was 80%. Further, of the 80% who had a first relapse, 80% had a second relapse. The rate of multiple relapses in this study was high. Of the 118 subjects at baseline, only 12 did not have a relapse during the 5-year follow-up period.

There was a higher rate of relapse in schizophrenia than in bipolar disorder, yet other studies have also shown that a cumulative switch and relapse rate in bipolar disorder is still about 60%.⁸ The rate of functional recovery is low in schizophrenia—38% for having intact functioning in the absence of symptomatic remission and about 17% for the convergence of functional recovery and symptomatic remission.

In the schizophrenia study,⁴ cognitive functioning after stabilization was the single strongest predictor of full recovery. In the bipolar study,¹ cognitive functioning was not reported and the determinants of lack of functional recovery are unknown. A return to baseline function still occurred in fewer than half of the bipolar patients, despite the fact that almost all of the subjects responded to their treatment and experienced syndromal recovery at some point during the follow-up. Cognitive functioning following stabilization in bipolar patients and its role in the determination of risk for impaired functional recovery is an area that needs further study.

IMPLICATIONS FOR TREATMENT

Early in the course of treatment of both schizophrenia and bipolar disorders, syndromal remission is easy to obtain and difficult to maintain. Even symptomatic remission is common in bipolar disorder, while relapse and switch rates are still very high. Patients with bipolar disorder may go through extended periods during which their symptoms do not meet the criteria for bipolar disorder or any major mental disorder. At the same time, functional recovery rates are extremely low across these two illnesses. In the study described earlier,¹ the criteria for functional recovery were minimal, yet most patients still did not meet those criteria. A return to baseline as a criterion for recovery may be a relatively low standard with early-onset illness, if the patient's life and functional status were not well developed in the first place.

Subsyndromal symptoms in bipolar disorder may have considerable short-term prognostic importance, particularly in the areas of quality of life, development of therapeutic alliances, acceptance of responsibility for management of the illness, and medication adherence. Patients who have residual depressive symptoms and reduced quality of life may discontinue use of their medications, and such discontinuation is the best predictor of worsening. Unfortunately, the data from this study are probably the best-case scenario data, because these are people experiencing their first episode. These are not

outcomes for people who already have a chronic, established course of bipolar disorder. The rate of functional recovery following an episode of bipolar disorder in people who have had several previous episodes is probably even lower, so clinicians must consider the possible adverse effects of partial compliance and the development of poor response and rapid cycling.

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

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