FUNCTIONAL IMPAIRMENT AND COGNITION IN BIPOLAR DISORDER

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Bipolar disorder is a common, chronic and severe mental disorder, affecting approximately 2% of the adult population. Bipolar disorder causes substantial psychosocial morbidity that frequently affects the patient's marriage, children, occupation, and other aspects of the patient's life. Few studies have examined the functional impairment in patients with affective illness. Earlier outcome studies of mania reported favorable long-term outcomes. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment. These low reports of functional recovery rates are particularly surprising. The basis for such limited functional recovery is not entirely clear. Factors associated with functional dysfunction include presence of interepisode symptoms, neuroleptic treatment, lower social economic class, and lower premorbid function. Cognitive dysfunction, a symptom domain of schizophrenia, has been identified as an important measure of outcome in the treatment of schizophrenia. Recently, there has been some suggestion that there may be impaired neuropsychological performance in euthymic patients with recurring mood disorders. Whether impaired neuropsychological performance in associated with the functional impairment in bipolar patients who have achieved syndromal recovery is an intriguing question. The literature on functional impairment and cognition in bipolar disorder is reviewed.

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PSYCHIATRIC QUARTERLY, Vol. 71, No. 4, Winter 2000
0033-2720/00/1200-0309$18.00/0

The outcome of mania has been studied ever since the diagnosis was first recognized. In these studies, much emphasis has been placed on recovery from major affective episodes (mania, depression, mixed states) but very little emphasis has been given to psychosocial outcomes in bipolar disorder patients. In the era prior to modern pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. Kraepelin in 1921 noted that manic or depressive episodes were periodic in nature, and typically were followed by a return to normal functioning. Similarly, in Rennie's 1942 study of 208 cases from 1913 to 1916, more than 90% of patients were reported to have recovered from an initial episode. Both Kraepelin and Rennie reported that remissions lasting for many years were not uncommon. In contrast, more modern studies do not describe such a favorable outcome in patients with bipolar disorder. Several of these studies describe that these patients have a significant degree of morbidity and dysfunction on follow-up (Bratfos and Haug, 1968; Tsuang et al., 1979; Dion et al., 1988; Harrow et al., 1990; Tohen et al., 1990; O'Connell et al., 1991; Carlson et al., 1974; Coryell et al., 1993, 1993; Goldberg et al., 1995; Gitlin et al., 1995; Strakowski et al., 1998; Keck et al., 1998; Tohen et al., 2000) (Table 1). This table presents the major findings about outcome in mania from a series of naturalistic follow-up studies during the past two decades. In general, the majority of studies, both short and long-term, have found that a high percentage of patients have impairment in at least one major area of overall functioning. Tsuang et al., 1979 found that occupational impairment was common and persistent in up to one-quarter of the patients' studied, even 30 years after an initial manic episode. Dion and colleagues (1988) carefully evaluated the functional outcome of 67 patients with bipolar disorder for 6 months following discharge. They found that symptomatic recovery preceded functional recovery in a majority of patients. At 6 months, only 40% were able to work or study and only 36% were able to live independently. Harrow et al., (1990) reported the long-term outcome of 100 patients hospitalized for acute mania and unipolar depression. These patients were systematically followed-up and evaluated on two occasions (at a mean of 2 years and again at 4.5 years following their index episode). Only 27% of bipolar disorder patients at 2 years and 41% of bipolar disorder patients at 4.5 years had good overall functioning. They found that many of these pa-

TABLE 1
Outcome Studies Reporting Functional Outcome in Patients with Affective Disorders

Investigators	*N*	*Follow-up Period*	*Comment*
Tsuang et al., 1979	100	30 years	24% had poor work functioning
Dion et al., 1988	67	6 months	67% had poor work functioning; those with multiple admissions had greatest impairment
Harrow et al., 1990	73	1.7 years	34% had very poor global functioning; outcome was poorer for BP than for UP
Tohen et al., 1990	75	4 years	28% were unable to work; 19% could not live independently at follow-up
O'Connell et al., 1991	248	1 year	19% had very poor outcome
Coryell et al., 1993	29	5 years	31% never achieved sustained recovery
Goldberg et al., 1995	51	4.6 years	22% had poor outcome; 14% persistent poor functioning at two follow-ups
Gitlin et al., 1995	62	4.3 years	35% had poor occupational functioning; 61% had only fair or poor social functioning
Strakowski et al., 1998	109	1 year	65% failed to achieve functional recovery; all subjects had prior hospitalizations
Keck et al., 1998	134	1 year	76% failed to achieve functional recovery; patients with mixed or mainic episodes at index did not differ in recovery rates at follow-up
Tohen et al., 2000	219	2 years	63% failed to reach functional recovery

Adapted from Goldberg and Harrow 1999.

tients receiving conventional treatment improved over the follow-up period, however, a subgroup approaching 60% still experienced poor adjustment in one or more areas of functioning. Tohen et al., (1990) followed 75 bipolar I disorder patients for 4-years whose index episode was manic. At follow-up they found that approximately 20% of the patients were unable to work, study or live independently. Coryell et al., (1993) examined the scope, severity, and persistence of psychosocial impairment arising from bipolar and unipolar affective disorder. Patients with bipolar (N = 148) or unipolar (N = 240) major affective disorder were assessed as they sought treatment and again after a 5-year follow-up. First-degree relatives who had no lifetime history of affective disorder were used as a comparison group. Relative to comparison subjects, affective disorder groups were significantly more likely to report declines in job status and income at the end of follow-up and significantly less likely to report improvements. The authors found that the psychosocial impairment associated with mania and major depression extends to essentially all areas of functioning and persists for years, even among individuals who experience sustained resolution of clinical symptoms (Coryell et al., 1993). Gitlin et al., (1995) in their bipolar clinic found that one-third of their patients had poor occupational functioning at an average of 4.3 years follow-up despite receiving contemporary treatments. Cooke and colleagues (1996), reported marked reductions in self-reported functioning and well being in 68 euthymic RDC bipolar disorder outpatients as measured by the Medical Outcomes Study questionnaire (MOS) questionnaire (SF-20). Patients' mean scores on the six SF-20 subscales fell within or below the range of mean scores reported for patients with chronic medical illness and major depression in the MOS. Robb and colleagues (1998) also studied euthymic outpatients with bipolar disorder to see if there were any gender differences in subjects' perception of well-being and functioning. The authors found that women with bipolar disorder compared to men were more likely to report an overall impairment in all MOS subscale scores with significant impairment in physical health and pain. Laroche et al., (1995) also found disruption of social functioning even during quasi-asymptomatic periods in patients with major affective disorders.

Even more recent studies suggest that up to 76% of patients with either bipolar disorder or affective psychoses fail to

achieve functional recovery at 12 and 24-months following their index manic episode (Keck et al., 1998; Strakowski et al., 1998; Tohen et al., 2000). Strakowski et al., (1998) reported that only 35% of 109 patients with affective psychosis [functional recovery: bipolar, 36%, major depression, 30%] achieved functional recovery by 12 months after their first hospitalization. Keck et al. (1998) reported that only 24% of patients with DSM-III-R bipolar I disorder achieved functional recovery at some time during the interval between hospital discharge and 12-month follow-up.

Recently Tohen and colleagues (2000) reported the syndromal and functional recovery rates among 219 psychotic affective disorder patients at 6 or 24 months after first-lifetime hospitalization. In this study, patients consecutively admitted for their first hospitalization of affective psychosis were recruited. Diagnostic, symptomatic, and functional evaluations were obtained at index hospitalization, 2, 6 and 24 months. Syndromal recovery was operationally defined as no longer meeting DSM-IV criteria for a manic or major depressive episode. Functional recovery was defined as the patient having returned to their baseline level of functioning. The authors found that most patients (97%) achieved syndromal recovery at 6 and 24-months post-admission, however, only 37% achieved functional recovery within the same period of time (Figure 1). During the period of the study (1989–1996), hospital length of stay declined progressively across study years by almost 4-fold from 45 days in 1989 to 12.5 days in 1996. The proportions of patients attaining both syndromal and functional recovery within 2 years of initial hospitalization remained quite stable across of study-entry despite a marked shortening of the length of stay. Apparently, shorter length of stay had neither an unfavorable nor a favorable effect on time-to-syndromal recovery or chances of functional recovery for most patients. It seems unlikely that shorter inpatient stays reflect improvements in therapeutics in recent years. More plausibly, patients probably continue to recover after hospitalization in alternative settings, including partial hospitalization, transitional care, or other ambulatory programs or even at home.

In summary, bipolar disorder, even in clinical remission appears to be associated with marked reductions in functioning and well-being, confirming the importance of the disorder as a major

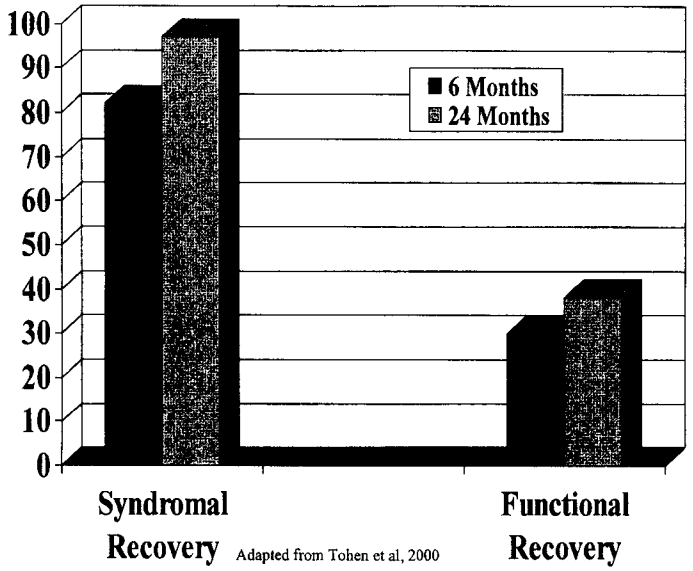

FIGURE 1. Percentage of patients with first-episode psychotic affective disorders who reached syndromal (N = 199) and functional (N = 181) recovery within 6 and 24 months after first lifetime hospitalization.

public health problem, meriting substantial resources for further research and treatment.

WHY THESE DIFFERENCES IN THE COURSE OF BIPOLAR DISORDER OF EARLIER COMPARED TO MORE MODERN STUDIES?

The reason for the discrepancies in outcome between earlier and more recent studies is unknown but probably is due to several factors including differences in research methodology used, difference in diagnostic criteria used, medication induced changes, psychiatric and medical comorbidity, alcohol and drugs and other as yet unidentified factors.

Differences in Research Designs and Diagnostic Criteria Used

Research designs and diagnostic criteria for mania and relapse have become more standardized. Many cases of major affective

illness with psychotic features probably have been included among persons diagnosed with schizophrenia earlier in this century, and the distinction between these major groups of psychotic syndromes may still be much less clear than is widely assumed (Hegarty et al., 1994). Misassignment between the schizophrenia and manic-depressive syndromes over the past century has probably biased estimates of recovery within both diagnostic categories in complex and poorly quantified ways (Hegarty et al., 1994). Diagnostic systems have shifted to include patients with more severe psychopathology and prominent psychosis as meeting criteria for a diagnosis of bipolar disorder.

Medication Induced Changes

Medication induced changes may be yet another factor in explaining the discrepancies in recovery rates between earlier and more recent studies. It is possible that as clinicians we have been contributing to a worsening of the course of illness by the indiscriminate and excessive long-term use of antidepressants in bipolar disorder. Angst (1985) reported that the switch rates into mania have increased by decade of treatment. In the analysis of studies of switch rates by Angst he found that in the pre-pharmacotherapy era the switch rates ranged between 3% and 4% and with the introduction of tricyclic antidepressants increased to approximately 8%. Bipolar disorder patients exposed to long-term use of antidepressants may also be at a higher risk of rapid cycling (Goodwin and Jamison, 1990). Furthermore, some authors have reported that long-term use of neuroleptics in bipolar patients is associated with an increased frequency of major depressive episodes (Kukopoulos, 1980) and lower functional recovery rates (Tohen et al., 1990). Recent studies suggest that a majority of bipolar disorder patients remain on conventional antipsychotic drugs for long periods of time following their hospitalization (reviewed in Zarate et al., 2000). This may in part explain why some patients have poor long-term functioning.

Substance Use Disorders

Substance use disorders have been reported to be associated with worse long-term outcome in patients with bipolar disorder by way

of producing mixed states, rapid cycling and an increased risk of suicide, rehospitalization and noncompliance (Mayfield and Coleman 1968; Himmelhoch et al., 1976; Keller et al., 1986; Morrison 1974; Tohen et al., 1990; Sonne et al., 1994; Keck et al., 1998; Goldberg et al., 1999). The reader may wish to refer to a more detailed review of substance use disorders and bipolar disorder (Tohen et al., 1998a).

HOW DO WE MEASURE OUTCOME?

There are many different ways of measuring outcome and each method may lead to a different set of conclusions. One way of measuring outcome is to determine the proportion of patients who achieve symptomatic/syndromal recovery after an index episode or the time it takes to reach this type of recovery. Another way of measuring outcome may be to examine the rates of relapse or recurrence after an index episode. Other methods include counting the number of affective episodes, estimating the duration of each episode, the number of hospitalizations at follow-up etc. Yet another less commonly used method of measuring outcome and perhaps a more meaningful way of estimating morbidity is combining both the counts of affective episode and subtle (subsyndromal) affective symptoms. This is referred to as cumulative morbidity.

Functional recovery in bipolar disorder has been described as the ability to achieve level of functioning that existed prior to the most recent episode (Tohen et al., 2000). Functioning is complex and involves many different domains including the capacity to work, capacity to live independently, capacity for recreation, capacity for romantic life, capacity to study, etc. Psychosocial/functional outcome uses a different set of observations and measures but typically evaluates patients in their major psychosocial domains. Researchers traditionally measure one or two elements of functioning and typically fail to take into account all the other elements necessary for optimal functioning. As a result, the method by which functional recovery is ascertained may lead to a different set of conclusions. Studies should measure all these different domains as a patient may do very well in one domain but very poorly in other domains. Also, it is important to determine

the context in which functional outcome is measured. For example, occupational outcome may vary by whether or not the patient is the owner of their business or not. If the patient owns their business, on evaluation they may be rated as having achieved "functional recovery" even if significant impairment in functioning is present. On the other hand, a patient may have fully recovered in terms of functioning but may not be permitted to return to work by their employer until more time has elapsed. The former example may be rated as doing well and the latter case as doing poorly when in fact the contrary may be the case. Also, a patient may be more reluctant to return to work if they are feeling embarrassed or ashamed of their recent manic behavior even though at present they may be functioning well.

The basis for such limited functional recovery is not entirely clear but has been reported to be associated with a number of different factors. These factors associated with functional dysfunction include the presence of interepisode symptoms, psychotic symptoms, medication effects (reviewed above), and lower premorbid function. We will review each of these different factors presumed to be etiologically related to these poor functional outcomes.

The Presence of Interepisode Symptoms as a Predictor of Poor Functional Outcome

The UCLA group reported on their findings on impaired functioning in bipolar disorder patients (Gitlin et al., 1985). During a 6-year period, 160 patients with DSM-IV bipolar I disorder were treated in their Affective Disorders Clinic for more than 3 months. Of these patients, 82 were treated for 2-years or more. Treatment was uncontrolled but the general philosophy was that maintenance treatment was virtually always indicated. They found that the likelihood of either a full manic or a full depressive episode within 5 years was 73%, with 37% of the relapses occurring in the first year. Of those who relapsed, 70% had multiple episodes. They used a cumulative psychopathology method as their outcome measure. Only 17% of patients were euthymic during the follow-up period. Thirty percent of the patients were significantly symptomatic for more than one-quarter of the follow-up period. Also in their study, they found that the number of major depressive epi-

sodes was associated with family dysfunction more than was the number of manic episodes. Similarly, social maladjustment was associated with the number of major depressive episodes more than with manic episodes. They found that the average mood scores were more highly correlated with poor psychosocial outcome than were the number of episodes. The authors suggest that cumulative psychopathology may more accurately represent the destructive process by which bipolar disorder leads to poor psychosocial function (Gitlin et al., 1995).

However, it remains unclear what the temporal relationship is between interepisode symptoms and the impairment of functioning. Is it that subsyndromes lead to a worsening of functioning or is the reverse true that poor functioning leads to demoralization, and low self-esteem resulting in depression?

The Presence of Psychotic Symptoms as a Predictor of Poor Functional Outcome

Rosen and colleagues (1983) examined the effects of psychosis on social outcome in bipolar I patients. They studied a total of 89 subjects of which 63 were psychotic and 26 were not psychotic. The psychotic group had significantly poorer outcome in terms of social functioning. Although current age, age at first treatment, and duration of illness distinguished the two groups of patients, statistical analyses indicated that these variables did not account for differences in social outcome. In contrast, MacQueen and colleagues (1997) did not find that psychosis at the index episode was associated with poor functional outcome.

Low Premorbid Functioning as a Predictor of Poor Functional Outcome

Cannon et al (Cannon et al., 1997) reported that impaired premorbid social functioning is not specific to schizophrenia and is also seen in bipolar disorder. The authors hypothesized that poor premorbid social adjustment is one manifestation of vulnerability to adult psychotic disorders. Recently Strakowski and colleagues published their findings on a 12-month outcome after a first hospitalization for affective psychosis (Strakowski et al., 1998). In

this study, 109 patients consecutively admitted for their first hospitalization of affective psychosis were recruited. Diagnostic, symptomatic, and functional evaluations were obtained at index hospitalization, 2, 6 and 12 months. The authors found that functional dysfunction was associated with low premorbid socioeconomic status.

Other Factors That Have Been Reported to Be Associated with Functional Impairment in Affectively Ill Patients

Clinical factors reported to be associated with poor functional recovery after initial hospitalization for first-episode psychotic affective disorders included long hospitalization, onset of age <30 years, Axis I comorbidity, and single marital status (Tohen et al., 2000). Relapse has been associated with poorer long-term psychosocial function in Bipolar I disorder patients (Solomon et al., 1996). Variables predictive of functional outcome among adolescents and young adults include diagnosis, symptom severity, duration of onset of symptoms, age of onset of symptoms, gender, stressful life events, premorbid functioning, and social supports (Henry and Coster 1996). Better psychosocial outcome has been reported to occur in patients in higher socioeconomic brackets compared to patients in lower brackets (Solomon et al., 1996), in patients receiving lithium doses that achieved standard serum levels compared to patients receiving doses that achieved low serum levels (above and beyond the effects of relapse prevention) (Solomon et al., 1996). An earlier study however, failed to find any differences in interepisode functioning between bipolar patients (N = 44) with plasma lithium levels above or below the median (Goodnick and Fieve, 1985).

CAN COGNITIVE DYSFUNCTION BE THE REASON FOR POOR PSYCHOSOCIAL/FUNCTIONAL OUTCOME?

Cognitive dysfunction, a symptom domain of schizophrenia, has been identified as an important measure of outcome in the treatment of this disorder. Many studies on cognition have been conducted in patients with schizophrenia. However, few studies have

been conducted in patients with affective disorders, particularly in patients with bipolar disorder. Cognitive functioning in the non-symptomatic phase and the long-term cognitive outcome of patients with mood disorders are both heuristic and important clinical issues in the study of mood disorders. Literature findings are inconsistent because of design confounds. Affective disorders typically have better outcomes than schizophrenia, although recent evidence suggests that some patients with affective disorder have a relatively poor outcome (Tohen et al., 2000), with cognitive impairments and persistent symptomatology. Cognitive impairment has been held to be uncommon in bipolar disorder. The nature and extent of neurocognitive dysfunction in persons with bipolar only recently has begun to be examined. Many neuropsychological studies have been conducted in patients with mood disorders and schizophrenia (Goodwin and Jamison, 1990). Earlier studies conducted prior to 1975 found no consistent findings in cognitive deficits in bipolar patients. Later studies examining cognition in affective disorder patients (reviewed by Goodwin and Jamison, 1990) generally found that patients with affective disorders had more neuropsychological impairment than normal controls but not as severe as patients with schizophrenia. This lack of findings may be largely the result of small patient samples studied, unspecified diagnosis used, and the lack of consistent measures used to evaluate cognition. Furthermore, a number of these studies included patients that were either in the acutely manic or depressed state or abusing alcohol or drugs. Also, it has been suggested that drug side effects may in part explain the cognitive deficits seen in bipolar disorder patients. Psychopharmacological treatment has been suggested to influence neuropsychological test performance with neuroleptics and anticholinergic drugs having the greatest effect (Bellini et al., 1988). However, one study (Joffe et al., 1988) did not find significant cognitive deficits to occur with the use of lithium and carbamazepine. In this study, cognitive functioning was assessed in medication-free as well as carbamazepine- and lithium-treated patients with manic-depressive illness. Across a range of tests measuring attention, concentration, visuomotor function, and memory, no significant differences were observed across the three patient groups as compared with control subjects without manic-depressive illness. The interpretation of such studies is difficult as clinical significant

levels of depression, psychosis or substance use disorders can account for most if not all of the cognitive deficits observed. Many of these later studies began to control for factors that may influence cognition such as the state of illness (acute mania and depression), the influence of psychoactive substances, the use of psychotropic medications. Savard and colleagues (1980) compared the cognitive functioning of unipolar and bipolar with the Halstead-Reitan category test when in an unmedicated acutely depressed phase of illness. Controls consisted of normal volunteers and spouses. Results showed that depressives in the acute depressed state made significantly more errors than did controls. Older bipolar patients made significantly more errors than younger bipolar or younger unipolar patients and controls. The authors concluded as early as in 1980 that impaired cognitive functioning may be a factor in the disability associated with the major affective disorders, in addition to the distorted affective component usually emphasized. More recently Coffman and colleagues (1990) found that there may be impaired neuropsychological performance even in euthymic patients with recurring mood disorders. They studied 30 ambulatory outpatients with bipolar disorder and compared them to normal controls. Bipolar disorder patients had greater levels of diffuse (generalized) cognitive impairment compared with controls. There was some suggestion of greater right hemisphere impairment in the bipolar group. In particular, the patient group differed from controls in nonverbal memory but did not differ in verbal memory. Another study also found impaired neuropsychological performance in euthymic patients with recurring mood disorders (Tham et al., 1997). In this study, 26 euthymic DSM-R recurring mood disorder patients were investigated by using the Synonym Reasoning and Block-Test Battery and a part of the Halstead-Reitan Test Battery. The authors found that the number of hospitalization episodes significantly correlated with: reasoning, general intelligence, Trail Making A (impairment was correlated with length of illness) and Trail Making B tests.

One study (Paradiso et al., 1997) addressed some of the concerns generated in the previous study by controlling for age, education, gender differences in neurobehavioral functioning, and diagnosis. Non-symptomatic patients with a history of chronic unipolar depression and bipolar affective disorder and healthy male individuals were administered neuropsychological tests to

assess attention, visual-motor tracking, executive abilities, and immediate verbal memory. Subjects had depression scores comparable to each other at the time of testing. Average disease duration was 8 years for unipolar and 11 years for bipolar patients. The authors found that unipolar patients were more impaired than healthy normal comparison subjects on measures of visual-motor sequencing (Trail Making Test A), executive function (Trail Making Test B, Stroop Test Color/Word Trial), and immediate memory and attention (WAIS Digit Symbol subtest). The cognitive disturbance found was the type seen with prefrontal dysfunction. However, the investigators did not find any differences between bipolar patients and normal comparison subjects in any of the selected measures. It is possible that the lack of cognitive deficits reported in these "non-symptomatic" bipolar disorder patients was due to the fact that they were not functionally impaired. There is no mention in this latter study as to the level of functioning of these patients at the time of the testing. In another study (Harvey et al., 1997), 50 chronically hospitalized geriatric patients with mood disorders (major depression or bipolar disorder) were compared on the clinical symptoms and aspects of cognitive impairment with 308 geriatric schizophrenic patients who were hospitalized at the same institution. The two samples were similar in current age and in premorbid education level. The authors found no overall differences in cognitive functioning between the groups, suggesting that cognitive impairment is present in poor-outcome patients with affective disorders as well as schizophrenia. Sax and colleagues (1998) compared the attentional performance in patients with a first-episode of affective psychosis (n = 27) compared to normal volunteers (n = 31) during acute and compensated states in order to determine whether changes in attentional functioning over time were accompanied by changes in the severity of psychotic or affective symptoms. Attentional performance was measured using the degraded-stimulus continuous Performance Test and symptoms were assessed at the time of index hospitalization, and 2 months after discharge. The authors found that the patients with an affective psychosis diagnosis performed significantly worse than controls at the initial testing but not at follow-up and concluded that attentional dysfunction is a state-dependent characteristic of mania. One study (Atre-Vaidya et al., 1998) examined the relationship among

poor functioning, cognition, and psychopathology in patients with bipolar disorder. In this study, the authors assessed 36 patients with bipolar mood disorder (23 Veterans Administration, 13 community) for the presence of psychopathology, cognitive deficits, and psychosocial impairment. The authors assessed psychopathology using screening and follow-up questions based on the Schedule for Affective Disorder and Schizophrenia, Lifetime Version, Schedule for the Assessment for Negative Symptoms, and Schedule for the Assessment of Positive Symptoms, and psychosensory features using the "Profile of Psychomotor Symptoms." The authors tested cognitive functioning in the following domains: 1) general intelligence and language, 2) verbal and visual memory, and 3) visuospatial functioning. They also measured and evaluated psychosocial functioning using a structured scale to assess maladjustment and an impairment rating scale. Patients with bipolar disorder showed significant impairment compared to age equivalent normals in several cognitive domains. Anhedonia was related to memory deficits. Memory deficits were also associated with poor psychosocial functioning. This study demonstrated that non demented, asymptomatic patients with bipolar disorder exhibit substantial cognitive deficits that are associated with poor functioning, and that anhedonia and avolition best predicts this outcome. In a more recent study, Van Gorp and colleagues (1998) compared 25 euthymic bipolar patients (12 with and 13 without a history of alcohol dependence) to 22 normal control subjects on a neuropsychological test battery assessing a range of cognitive domains. They found that bipolar patients with and without alcohol dependence performed more poorly than controls on tests of verbal memory. Furthermore, bipolar subjects with a history of alcohol dependence had additional decrements in executive (i.e., frontal lobe) functions when compared with controls. In addition, the lifetime months of mania and depression (cumulative morbidity) were negatively correlated with performance in verbal memory and several executive function measures.

Cognitive dysfunction has been identified as an important measure of outcome in the treatment of schizophrenia. In schizophrenic patients, drug-mediated symptom improvement typically fails to associate with modifications of cognitive dysfunction. A paradigm shift is now required in the conceptualiza-

tion of treatment success away from symptom decrement and toward treatments that improve cognition in patients with schizophrenia (Hawkins et al., 1999). Clozapine, risperidone and olanzapine have been shown to provide benefits in several domains of cognitive function in patients with schizophrenia (Meltzer and McGurk 1999; Purdon et al., 2000). Clozapine treatment has been shown to provide a significantly greater improvement in several domains of cognitive function, especially attention and verbal fluency, compared with conventional neuroleptics, whereas risperidone appears to have a beneficial effect on working memory (Meltzer et al., 1996). Also, schizophrenic patients taking clozapine and risperidone have been reported to show better performance on maze tasks than untreated patients or patients taking conventional neuroleptics. In particular, patients treated with risperidone or clozapine were better able to maintain motor coordination while they focused on the more complex "frontal" maze tasks which required sequencing and planning (Gallhofer et al., 1998). These results have been speculated to be because of the normalization of dopamine function by clozapine and antagonism of 5HT2 receptors (Sharma and Mockler, 1998).

Low rates of functional recovery underscores the importance of including functional as well as symptomatic assessments in the comprehensive evaluation of newly psychotic patients, with more explicit differential attention to those who are not progressing rapidly toward functional as well as syndromal recovery. Such slowly progressing or poorer prognosis patients with psychotic affective illnesses are likely to require more intensive or structured aftercare, and perhaps early consideration of treatment advanced antipsychotic agents, as well as improved psychosocial interventions, including more effective rehabilitation efforts targeted to modify specific target disabilities. Cognitive deficits in schizophrenic patients have been shown to be highly associated with poor outcome even more than positive and negative symptoms. Recently, there has been some suggestion that there may be impairment of cognition in patients with bipolar disorder. Whether this is the case and whether this deficit in cognition is associated with the impairment in functioning seen in bipolar patients achieving syndromal recovery is an intriguing question.

As reviewed above, there is some evidence that euthymic patients with recurring mood disorders may experience impaired neuropsychological performance. Whether or not deficits in neuropsychological performance are associated with functional impairment in bipolar patients who have achieved syndromal recovery is an intriguing question and has yet not been adequately examined. Several studies examining the efficacy of atypical antipsychotic drugs in bipolar disorder have reported improvement in functioning as the affective symptoms resolve (Banov et al., 1994; Ghaemi et al., 1997; Segal et al., 1998; Tohen et al., 1999). Because antipsychotic drugs have antimanic and other thymoleptic properties in bipolar disorder patients and improve functioning and cognition in patients with schizophrenia, it seems reasonable to speculate that atypical antipsychotic drugs may help improve functional impairment in bipolar disorder patients.

CONCLUSIONS

Converging evidence suggests that psychosocial outcome of treated bipolar patients is not nearly as optimistic as expected. Cumulative psychopathology probably more strongly predicts poor psychosocial outcome than does the number of episodes. An intriguing question is whether clinicians should treat affective sub-syndromes more aggressively as these symptoms may be associated with poor functioning. However, if the residual symptoms are depressive in origin the use of antidepressants could potentially accelerate the illness or induce a switch into mania. It also seems possible that cognitive dysfunction may be partly responsible for these low functional recovery rates seen in bipolar patients even after long periods of time. Further studies are required to clarify the relationship between functional impairment, subsyndromes, and cognition.

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