Curr Psychiatry Rep (2011) 13:504–512
DOI 10.1007/s11920-011-0227-x

Functional Impairment, Stress, and Psychosocial Intervention in Bipolar Disorder

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Published online: 10 August 2011

Abstract The longitudinal course of bipolar disorder (BD) is highly impairing. This article reviews recent research on functional impairment in the course of BD, the roles of social and intrafamilial stress in relapse and recovery, and the role of adjunctive psychosocial interventions in reducing risk and enhancing functioning. Comparative findings in adult and childhood BD are highlighted. Life events and family-expressed emotion have emerged as significant predictors of the course of BD. Studies of social information processing suggest that impairments in the recognition of facial emotions may characterize both adult- and early-onset bipolar patients. Newly developed psychosocial interventions, particularly those that focus on family and social relationships, are associated with more rapid recovery from episodes and better psychosocial functioning. Family-based psychoeducational approaches are promising as early interventions for children with BD or children at risk of developing the disorder. For adults, interpersonal therapy, mindfulness-based strategies, and cognitive remediation may offer promise in enhancing functioning.

Keywords Functional impairment · Stress · Bipolar disorder · Expressed emotion · Psychosocial treatment · Psychosocial intervention · Family therapy · Interpersonal and social rhythm therapy · Cognitive-behavioral therapy · Mindfulness · Vocational functioning · Cognitive remediation

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Introduction

Bipolar I or II disorder (BD) affects 2% of the adult US population, and subthreshold forms affect another 2.4% [1, 2••]. Patients with BD I experience significant symptoms during approximately 50% of the weeks in their lives, with about three times as many weeks in states of depression as in states of mania or mood cycling [3]. The significant effects of BD on interpersonal functioning in the spheres of work, social, and family life have been well-documented in recent longitudinal studies [4, 5••]. The World Mental Health Initiative, which surveyed more than 8,000 people with BD, concluded that the illness is associated with a greater loss of disability-adjusted life-years than all forms of cancer or major neurological disease [2••]. Less than half of those with lifetime bipolar spectrum diagnoses receive any treatment, and in lower-income countries, the estimates are closer to 25% [2••].

Patients with BD who have onset before age 18 years—the median age at onset of the illness—have more severe courses of illness and are more functionally impaired over time than patients with onset after age 18 years [6]. Childhood-onset patients with BD show recurrent course patterns, with frequent switches of polarity, lengthy episodes, mixed mood presentations, and severe social, academic, and family consequences [7, 8••, 9, 10••].

The environmental context in which BD waxes and wanes appears to be quite important in determining outcomes such as relapse likelihood, symptom severity, and level of functioning. Certain types of life events and measures of family impairment have been investigated in relation to relapse and recovery [11]. Psychosocial interventions—particularly those that are psychoeducational, enhance patients' interpersonal skills, and enhance the ability to recognize prodromal signs of relapse—are

effective adjuncts to pharmacotherapy in hastening recovery, delaying recurrences, and improving functional outcomes [12].

This article examines three interrelated questions:

1. Which functional disabilities accompany BD, and which variables determine the degree of disability?
2. To what extent is stress in patients' social or familial environments associated with the symptomatic or functional course of the disorder?
3. To what degree and in which domains of outcome can psychosocial interventions augment pharmacotherapy? This review surveys findings relevant to both adult and childhood BD patients.

Work, Family, and Social Impairment

Most patients with BD experience impairments in social, occupational, and familial functioning even when euthymic [13]. The National Institute of Mental Health (NIMH) Collaborative Depression Study, a 15-year follow-up of 155 patients with BD I, 133 with BD II, and 358 with major depressive disorder, revealed that mood disorder patients experienced some degree of disability in more than half of the months followed [5••]. Patients with BD I were the most impaired in terms of work functioning, being fully unable to work during 30% of the follow-up months, compared with 20% of follow-up months in BD II and 21% in major depressive patients. In the Stanley Collaborative Network study survey of 253 patients with BD I and BD II, only 33% worked full-time, and 9% worked part-time. Fully 57% reported being unable to work or worked only in sheltered settings [14]. Work impairment is at least in part attributable to problems with attention, memory, or executive functioning, which are impaired even when patients are clinically stable [15, 16]. Many years after a manic episode, patients with BD have impairments in verbal learning and processing speed that are predictive of the degree of functional disability [4].

Longitudinal studies indicate that children with *DSM-IV* manic or mixed episodes have long-term impairments in social and academic functioning [8••, 9, 10••]. Children with "prodromal" or "high-risk" forms of BD, such as brief and recurrent manic or hypomanic episodes with a clear change in functioning, are just as impaired as children with full BD I or BD II disorder over 2- to 4-year follow-ups [7, 8••]. Like bipolar adults, children with BD have significant trait-like cognitive impairments, including problems in executive functioning, verbal memory, response flexibility, processing speed, reversal learning, and set shifting [17].

Several large-scale studies indicate that residual depressive symptoms are the strongest determinants of functional impairment. In the NIMH Collaborative study, functional impairment increased over time with each increment in depressive symptom severity [13]. In the World Mental Health Initiative, 74% of the respondents with current depression and 51% of the respondents with current mania reported major role impairment [2••]. The relationship between mood symptoms and degree of impairment appears to be bidirectional, however. Impairment is often the direct result of symptoms, but impairment can increase the speed of recurrence or the severity of depressive symptoms [18]. For example, low social support, particularly during or after an acute episode, is a strong predictor of the severity of subsequent depressive symptoms [19•, 20].

Psychosocial Predictors of the Course of Bipolar Disorder

Life Events Research

Psychosocial stressors in the domains of life events and family conflict or criticism are among the most consistent predictors of the timing of recurrences and the degree of recovery from episodes. Cross-sectional studies consistently find that negative life events are equally common before episodes of BD depression and unipolar depression [21]. In longitudinal studies, negative life events are associated with slower recovery from BD depression and increases in depression over time [22, 23].

Two theories have been proposed to explain the role of psychosocial stress in mania: goal dysregulation and sleep/schedule disruption. The goal dysregulation model emphasizes that even when they are not in an episode, patients with BD have stronger responses to rewarding stimuli [24]. As patients with BD become more and more engaged with a goal (eg, career advancement), they experience increases in confidence, attend more to positive stimuli, and underemphasize the possibility of negative consequences to their actions. Life events that accelerate goal engagement (eg, starting a new relationship, getting a job promotion) predict increases in manic symptoms, but not depressive symptoms [23, 25]. Among college students with subthreshold BDs, preparing for and completing final examinations is associated with an increase in hypomanic, but not depressive symptoms [26].

It has long been known that manic episodes are often preceded by life events that interfere with sleep (eg, transatlantic flights, childbearing) [27–29]. More recent research has examined whether sleep disruption is part of a broader problem with the regularity of daily and nightly routines. One study documented that individuals with BD have more variability in their daily schedules than healthy controls, although variability in daily routines was

independent of sleep disturbance [30]. In a study of 414 undergraduate students, participants with cyclothymic disorder or BD II reported fewer regular daily activities than healthy controls. In an average 33-month follow-up, those students with less rhythm regularity had shorter intervals before onset of a first depressive or (hypo)manic episode [31]. As discussed subsequently, inconsistent daily or nightly routines are amenable to regularization through psychosocial intervention, as emphasized in one model of intervention, interpersonal and social rhythm therapy (IPSRT) [32••].

Family Stress and Impairment

Studies of family stress and its association with the course of BD have focused on the construct of expressed emotion (EE), a set of caregiver behaviors that has been well-studied in schizophrenia and major depressive disorder [33]. EE, which is assessed by a clinical interviewer, refers to the expression of critical attitudes, hostility, or emotional overinvolvement (overprotectiveness) among the caregivers of patients who are in an acute episode of mood or psychotic disorder. The significance of EE is a prognostic one: patients who have been ill recently and who recover in high-EE households are at two to three times greater risk of relapse in the next year than patients who recover in low-EE (less critical or protective) households [34].

Several studies of EE have been conducted in BD, and all indicate that adult patients whose familial caregivers express high EE attitudes have higher rates of relapse or more severe mood symptoms over 9-month to 2-year periods than patients whose caregivers express low-EE attitudes [11]. Some, but not all studies have found a stronger impact of caregiver EE on patients' depressive symptoms than on their manic symptoms [35, 36].

The causal pathways that link caregiver EE with patient relapses are a matter of debate. Some studies indicate that high-EE caregivers are more likely to attribute the negative behaviors of patients to internal, controllable, and personal factors, whereas low-EE caregivers are more likely to attribute negative patient behaviors to external, uncontrollable, or universal factors [34, 37]. Thus, behaviors that may be part of the illness (eg, irritability, withdrawal) are sometimes viewed by caregivers as personality flaws.

Other studies focus on the patterns of family interaction that accompany EE attitudes in BD. Families with high EE are often locked into negatively escalating cycles of communication in which criticism and counter-criticism among family members and patients become highly reciprocal and mutually influential, leading to increases in patients' mood symptoms [38, 39]. A construct similar to EE—negative affective style, measured from parent/offspring interactional behaviors—predicted poorer social functioning in a 9-month follow-up of young adults with BD I following hospitalization for a manic episode [40].

The research on EE suggests that modifying the emotionally charged environment of the family during the postepisode phases may hasten patient recovery and delay recurrences. These issues are addressed in one model of integrated treatment for BD: family-focused therapy (FFT) [41].

Family Risk Processes in Childhood-onset Bipolar Disorder

The family environment has important risk or protective properties early in the symptomatic course of BD as well. One study found that adolescent BD patients who had high-EE parents and who were undergoing treatment had more persistent mood symptoms over 2 years than adolescents who had low-EE parents [42]. In one study, parents of BD adolescents—all of whom had had a recent episode of depression, mania, or hypomania—reported lower family cohesion and adaptability than parents of healthy adolescents (as reported in normative scale data) [43]. Parents rated high in EE reported lower levels of family cohesion and adaptability and higher levels of conflict than parents rated low in EE [43].

Mother/child relationships in childhood-onset BD are characterized by less warmth, greater tension, greater conflict, and more hostility than mother/child relationships in healthy control children or children with attention-deficit/hyperactivity disorder [44, 45]. Low maternal warmth—based on the self-reports of children and their mothers—was associated with a shorter time to manic recurrence and more weeks ill with mania in an 8-year follow-up of pediatric and early-adolescent BD patients [10••].

One large-scale (N=272), cross-sectional study of offspring of parents with mood disorders found a direct relationship between parental diagnoses and child diagnoses [46]. When the child had BD, the association between parental and child diagnoses was mediated by whether parents reported high levels of family conflict. Thus, parental diagnoses and family impairment may contribute jointly to child functioning.

Most of these studies could not fully disentangle the behavior of parents from the concurrent symptom states of children. Clearly, raising a symptomatic child with BD would lead to decreases in warmth and cohesion and increases in conflict in even the healthiest of families.

Processing of Social Information

A recent development in research on BD has been the investigation of social information processing styles. Social cognition paradigms—studies of how interpersonal data are processed at the cognitive, affective, and neural levels—

have long been fruitful in social psychology and have only recently made their way into studies of psychiatric disorders [47].

The processing of social information at the neural level may help clarify why family conflict or other interpersonal stressors are associated with mood deterioration among bipolar or other patients with mood disorders. Patients may have impaired perceptions of the motives, emotional states, or intentions of their family members or other significant people, and in turn, these misperceptions may affect their response choices. Several studies have undertaken an examination of neural activation in response to social stimuli in adult or childhood mood disorders.

One novel experiment examined differences between individuals in high- and low-EE families in terms of how criticisms are processed at the neural level [48]. College students with a history of depression listened to tapes of their parents criticizing them or expressing positive or neutral statements while the students were undergoing functional MRI scans. Students with a depression history were less able to recruit the dorsolateral prefrontal cortex when hearing criticisms than college students with no depression history. Similar experimental paradigms have been conducted in patients with borderline personality disorder [49] and schizophrenia [50], but not among patients with BD.

In BD, the focus of social information processing studies has been on recognition of facial emotions. The accurate perception of facial emotions is believed to be key to social competence and conflict resolution, as one must code subtle changes in another's emotions in order to respond effectively [51••]. Bipolar adults show impairments in the processing of facial emotions, although the nature, specificity, and persistence of these deficits vary across studies [52, 53].

Youth with BD make more errors on facial emotion recognition tasks than healthy controls or youth with major depression or attention-deficit/hyperactivity disorder across a variety of facial emotions and types of tasks [51, 54–58]. Similar to children who have experienced trauma or abuse [59], children with BD are especially likely to misclassify neutral facial expressions as hostile and threatening, even though they do not rate angry faces as more angry than healthy children do [57].

Rich and colleagues [51••] compared children with "narrow spectrum" BD (ie, bipolar I or II with elation or grandiosity), children with severe mood dysregulation (chronic irritability and hyperarousal), and healthy control children on a task involving rating gradations of different facial emotions (happiness, surprise, fear, sadness, anger, and disgust). The task required that participants indicate when they were certain of the emotion being expressed as the faces "morphed" from neutral to full expressions of emotion. Regardless of the facial emotion depicted, BD youth who were in a hypomanic or mixed state required more intense facial expressions before they were able to accurately identify the emotion than did control children. Importantly, impaired face emotion labeling predicted the degree to which the youth with BD showed social reciprocity skill deficits—the capacity to process social information and enact responses that fit the situation. A second study showed that euthymic BD youth also required more intense stimuli than healthy controls before they could correctly recognize an emotion [55].

Progress has been made in clarifying the neural circuitry underlying facial affect labeling. Using functional MRI, Rich et al. [57] found that a subcortical limbic circuit was activated among youth with BD during a task involving judging facial emotions versus a control face-rating task. When rating facial hostility, the youth with BD had greater activation in the left amygdala, nucleus accumbens, putamen, and ventral prefrontal cortex than age- and gender-matched healthy controls. When rating their fear of the face, the youth with BD showed greater activation in the left amygdala and bilateral accumbens.

Thus, most studies have found that BD youth misinterpret emotional faces, misidentify threat in neutral faces, and, when they accurately identify an emotion, require more intense displays of the emotion than are typical in real life social situations. No study to date has demonstrated that emotion labeling deficits predict the onset of BD among genetically at-risk youth. However, offspring of parents with BD show face processing deficits similar to those of youth with BD, suggesting that abnormal facial emotion processing may be an endophenotype for BD [54, 55].

It is not clear whether pediatric BD patients have difficulty reading the emotions expressed by their parents; the face emotion labeling tasks use standard stimuli rather than faces of adults known to the child. Theoretically, the degree to which BD youth have biased perceptions of their parents' facial emotions may correlate with whether parents express critical comments toward the child, or whether dyadic interactions routinely escalate into conflicts. When both the parent and child suffer from BD, difficulty with emotion labeling may be bidirectional.

Psychosocial Intervention to Stabilize Symptoms and Enhance Functioning

Research on the role of psychosocial stress in the course of BD, combined with evidence that patients with BD have biased perceptions of social information suggest that patients may benefit from psychotherapies that focus on emotion perception and regulation in interpersonal contexts. There are 20 randomized trials that support the

effectiveness of adjunctive family, group, interpersonal, and cognitive-behavioral approaches to relapse prevention and episode stabilization over 1- to 2-year intervals [12, 60]. A meta-analysis by Scott [61] found that in combination with pharmacotherapy, psychotherapy reduces the risk of any type of mood relapse over 1- to 2-year periods relative to comparison conditions (OR, 0.57; 95% CI, 0.39–0.82) and enhances social functioning (OR, 1.2; 95% CI, 0.3–2.1). Virtually all effective psychotherapies for BD incorporate significant elements of psychoeducation: the provision of information about coping with the disorder; personalizing this information to the patient; and actively encouraging the practice of illness management strategies, such as the ability to recognize and intervene early with prodromal signs of relapse.

The existing approaches are more varied in the degree to which they address the social, familial, or work impairments characteristic of BD. Cognitive-behavioral therapy (CBT) uses cognitive restructuring to help patients evaluate and restructure their core assumptions about relationships [62]. IPSRT uses social problem solving, clarification, and interpretation to help patients grasp the ways in which their mood states affect their relationships, and how their relationships affect their mood fluctuations [63]. FFT uses communication and problem-solving skills training to enhance functioning within the family unit [41]. Group psychoeducation focuses on skills for managing the disorder after an episode, with feedback from fellow patients in a mutually supportive setting [64, 65].

A recent large-scale trial of IPSRT versus a comparison supportive intervention (active clinical management) as an adjunct to pharmacotherapy revealed preventive effects on recurrence during maintenance therapy that could be attributed to earlier improvements in the regularity of sleep/wake rhythms [66]. Moreover, patients in IPSRT showed better vocational functioning during acute treatment than patients who received clinical management, although the clinical management patients "caught up" during maintenance treatment [32••]. It is possible that interpersonally oriented therapy helps patients who are recovering from an episode to manage their moods when coping with provocations in work settings.

The comparative effects of several different forms of psychotherapy were examined in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a comparative effectiveness trial conducted across 15 US sites [67, 68]. STEP-BD examined 293 BD I and BD II patients who began in an episode of depression. Patients were randomly assigned to up to 30 sessions of CBT, IPSRT, FFT, or a 3-session psychoeducational comparison called collaborative care. All patients received best-practice pharmacotherapy. Over 1 year, patients who received one of the three intensive therapies had higher rates of recovery and more rapid recoveries from depression (median, 169 days) than patients in collaborative care (median, 279 days). Patients in intensive therapy were 1.58 times more likely to be clinically well in any given month of the study than patients in collaborative care. Moreover, patients in intensive therapy showed better overall functioning, relationship functioning, and life satisfaction scores over 9 months, even after concurrent levels of depression were statistically controlled. There were no differential effects of any of the psychosocial interventions on vocational functioning [67].

Application of Psychosocial Interventions to Childhood Bipolar Disorder Patients

Various psychosocial programs have been adapted to the needs of younger patients with BD, but to date, there are only two randomized trials. FFT was tested in a randomized trial involving 58 youth with BD I, BD II, or not-otherwise-specified disorder [69•]. Across two sites, adolescents were randomly assigned to FFT (21 sessions in 9 months) plus pharmacotherapy or enhanced care (3 sessions of psychoeducation) plus pharmacotherapy, and observed over 2 years. Adolescents in FFT showed a more rapid and complete remission of depressive symptoms and less time in acute states of depression at follow-up than patients in enhanced care. FFT was only effective in stabilizing mania symptoms over 2 years among patients in high-EE families. A post hoc analysis revealed higher life satisfaction scores over time in adolescents who received the full family treatment.

A large-scale (N=165), 18-month, wait-list trial of multifamily group psychoeducational therapy for children (ages 8–12 years) with bipolar (70%) and unipolar (30%) disorders verified the effectiveness of intensive family approaches [70•]. Participants were randomly assigned to receive a 6-month psychoeducational treatment immediately or 1 year after entering the study. Children in the immediate treatment group showed greater improvements on an overall mood severity index than children whose treatment was delayed. The children in the wait-listed families showed similar levels of improvement after they received the intervention 1 year later. Hence, family psychoeducation appears to be an effective early intervention for youth with early-onset BD, although the most cost-effective length and format have not been clarified.

Conclusions

Research on the course of BD continues to document high rates of recurrences over time. Psychosocial stress factors, including life events and high EE from caregivers, are often

precipitants of symptom exacerbations. Fortunately, new psychosocial interventions, notably FFT, IPSRT, CBT, and group psychoeducation, have been shown to augment the impact of pharmacotherapy in improving symptomatic outcomes.

Unfortunately, many patients with BD, even those who conscientiously take medications and attend therapy sessions, are left with the question posed by Jack Nicholson in the famous 1997 movie of nearly the same name: is this as good as it gets? The course of the illness is accompanied by significant impairment in work, social, and family functioning, and low quality of life. We clearly need to do much better in enhancing patients' ability to find meaningful work, friendships, and satisfaction in their spousal and parenting roles despite their residual depressive symptoms and ongoing neuropsychological impairments. Our limitations in treating children with BD with pharmacotherapy or psychotherapy are particularly sobering, with many children requiring specialized schooling, residential treatment, or multiple medications [8••].

Novel psychosocial approaches in BD include mindfulness-based group therapy and dialectical behavior therapy, which are just beginning to be applied to adults and children with BD [71, 72]. These approaches teach behavioral strategies to modulate affective intensity and duration when patients are in interpersonally stressful circumstances. Relevant emotional regulation strategies include meditation, distraction, interpersonal skills training, and cognitive restructuring. Open trial data on these approaches suggest substantial improvements in symptoms over pre-/post-treatment intervals [71, 72]. Larger-scale randomized studies with ecologically valid outcome variables (eg, social performance in high-stress situations) will be required to show the generalizability of new emotion regulation skills across situations.

It is possible that cognitive remediation programs such as those used in the treatment of schizophrenia [73] will prove effective in enhancing vocational functioning in BD patients after a mood episode. One such approach is under development [74•]. This approach consists of 14 individual sessions in 4 months that focus on mood monitoring and cognitive restructuring to manage residual depressive symptoms; training in organization, planning, and time management; structuring tasks to maximize one's concentration abilities; and the use of internal or external reminder cues to improve memory. In a 7-month open trial, adult BD patients showed improvements in depressive symptoms, occupational functioning, and overall psychosocial functioning. It may be that cognitive remediation training will be particularly useful for childhood or adult BD patients with comorbid attention-deficit/hyperactivity disorders.

Finally, little is known about whether interventions applied before the onset of BD have a long-term benefit on psychosocial functioning. Randomized controlled data on the efficacy of pharmacotherapy in delaying or preventing the onset of BD are inconclusive [75, 76]. However, there are hopeful findings from the psychosocial arena. In a post hoc analysis of the multifamily group trial, Nadkarni and Fristad [77•] found that 44% of youth with depressive spectrum disorders and transient manic symptoms developed BD I/II (32%) or BD not otherwise specified (12%) in 18 months. However, the rate of conversion to BD spectrum disorder among youth who received 6 months of multifamily group psychoeducation was 16%, compared with 60% who were assigned to the 1-year wait list.

An adaptation of the FFT approach was recently applied to offspring (ages 9–17 years) who had parents with BD and who had manic or depressive symptoms that fell short of meeting the full *DSM-IV* criteria for BD I or BD II [78•]. In addition to psychoeducation, the approach included exercises to assist youth in responding to emotionally salient communication from their parents or siblings and developing alternate response strategies. In a small-scale open trial, high-risk youth showed improvements in depression, mania, and global functioning in 1 year. A controlled trial of FFT for youth at high risk of BD is now in progress [79]. Possibly, early psychosocial interventions to reduce interpersonal stress and conflict through enhancing emotion regulation skills in high-risk youth and parent(s) will decrease the child's liability toward onset of BD and its functional disabilities and, by extension, improve quality of life.

Acknowledgment This research was funded by National Institute of Mental Health grants R01-MH073871, R34-MH077856, and R21-MH62555, and a grant from the Danny Alberts Foundation. Dr. Miklowitz has also received research grant support from the Deutsch, Kayne, and Knapp Foundations.

Disclosure Dr. Miklowitz receives book royalties from Guilford Press and John Wiley and Sons and has had travel/accommodations expenses covered by the International Society for Bipolar Disorders and the American Association of Child and Adolescent Psychiatry.

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