Functioning and Disability in Bipolar Disorder: An Extensive Review

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Abstract

Background: Bipolar disorder has generally been regarded as having a better functional outcome than schizophrenia. However, studies have suggested low functioning in bipolar patients even when they are in clinical remission. Our aim was to determine the degree of functioning and disability in bipolar patients. Secondly, we reviewed factors potentially associated with the low functioning of bipolar patients.

Method: The authors conducted an extensive Medline and Pubmed search of the published literature from 1980 up to December 2007, using a variety of search terms to find relevant articles. Bibliographies of retrieved papers were further analysed for publications of interest. Articles that reported clinically significant findings on functioning and disability, and research reports were reviewed in detail.

Results: From these articles, we determined that bipolar disorder is associated with significant impairment in work, family and social life, beyond the acute phases of the illness. The aspects that appear to increase the risk of low functioning and disability in bipolar patients are mainly subsyndromal symptoms and neurocognitive impairment, among others. Conclusions: Suitable pharmacological and psychological interventions may improve the level of functioning and reduce the disability in bipolar patients. Potential targets to be considered for intervention should be residual symptoms, comorbid conditions and neurocognitive deficits. Further research is required to better identify the factors that best predict functioning in bipolar patients.

Key Words

Bipolar disorder · Functioning in remission · Disability in remission

Introduction

Bipolar disorder is a multidimensional condition, involving a complex and dynamic interaction between biological and psychosocial factors [1]. Bipolar disorders constitute 1 of the 10 leading causes of disability worldwide [2]. Bipolar disorders have generally been regarded as having a better course and outcome than schizophrenia. However, a substantial proportion of bipolar patients show persistent subsyndromal symptoms, and most individuals with bipolar disorder are symptomatic more than half of their lives despite receiving pharmacological treatment [3, 4]. Even those patients who achieve full clinical remission show difficulties in making a complete func-
tional recovery, returning to their premorbid level of functioning [5–18]. Nevertheless, psychosocial outcomes in patients with bipolar disorder have generally received less attention than those in patients with psychosis [7].

Based on the biopsychosocial model of health, the new International Classification of Functioning, Disability and Health (http://www.who.int/classification/icf) [19] provides a new international framework to systematically describe the functioning of individuals across different domains and allows the study of the interaction between symptomatology and environmental factors. This will be a valuable tool for gathering and analysing population health information from around the world, as well as clinical, research, policy development and other uses, and will provide the basis for the standardization of data concerning all aspects of human functioning and disability [20, 21]. Functioning is a complex concept, since it involves the capacity to work, study, live independently and engage in recreational activities and interpersonal relationships [7]. Disability is defined as a difficulty in functioning at the body, person or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors [22].

Despite the gap between clinical and functional recovery, few studies have examined those factors that may be involved in the functional outcome of bipolar disorder [23]. Among the factors that may affect the outcome of bipolar disorder are clinical variables, such as age at onset, frequency of episodes, subclinical symptoms, rapid cycling, psychotic symptoms, mixed symptoms [24, 25], psychiatric and medical comorbidity [26–28], treatment compliance [29, 30] and other factors such as environmental variables like social support [9, 31, 32] or life events [33]. The impact of neurocognitive impairment has not been well investigated, but it probably constitutes a good predictor of functioning [23, 34, 35]. In addition, pharmacological factors, such as side effects, may also affect functioning in bipolar patients [36, 37].

The main aim of this review was to determine the level of functioning and disability in bipolar patients, focusing on 3 main areas of functioning that have been suggested to be impaired in these patients: work, social and family functioning. The review also focuses on the impact of cognitive factors and the relationship between clinical, cognitive and functional issues. We also aimed to establish which factors are the most common influences on low functioning in bipolar patients. To our knowledge, this is the first review focused on both functioning and its correlates in bipolar disorder.

**Methods**

A review of the studies on Medline/Pubmed search from January 1980 to December 2007 was carried out. We selected documents containing, in the title and abstract sections, the descriptors ‘bipolar disorder’, ‘bipolar patient’, ‘functioning’, ‘functional outcome’, ‘functional recovery’, ‘disability’, ‘social functioning’, ‘psychosocial functioning’, ‘work functioning’, ‘occupational functioning’, ‘family functioning’, ‘cognitive impairment’, ‘neurocognitive’ or ‘neuropsychol’. Abstracts and titles were used to determine whether the reference might be relevant to the review, and full texts of potentially relevant articles were retrieved to assess the article for inclusion. The same procedure was followed for the different sections.

The articles were selected if they met the following quality criteria: bipolar I or II patients, with or without an acute affective episode, cross-sectional or longitudinal studies, clinical trials, randomized clinical trials, systematic reviews and meta-analyses, including standardized diagnostic criteria, outcome measures, such as Diagnostic and Statistical Manual of Mental Disorders, Positive and Negative Syndrome Scale, Young Mania Rating Scale, Hamilton Depression Rating Scale, and well-established measures of functioning and disability, including quality of life measures like for instance World Health Organization Disability Assessment Schedules I or II, Global Assessment of Functioning (GAF), 36- and 20-item Short-Form Health Surveys or the Simpson-Angus Scale, using clear descriptive and comparative statistical methods.

Finally, the reference lists of retrieved articles were checked for any further relevant citations. Articles that reported clinically significant findings on functioning and disability in bipolar disorder, as judged by the authors, were reviewed in detail. No meta-analyses were found on these issues, and only a systematic review specifically addressed to health-related quality of life, work impairment and healthcare costs in bipolar disorder was obtained in the search [37].

**Results**

As can be seen in table 1, the most relevant longitudinal studies on functioning and disability are shown. This article is therefore divided into two sections. The first section explores functioning and disability in different areas considered to be of potential interest in bipolar disorder, the second section explores correlates of low functioning or disability.

**Functional Outcome in Bipolar Disorders**

There are several areas of functioning that may be impaired in bipolar disorder. We are going to focus on those areas that seem to be more impaired, such as social functioning, work functioning and family functioning.
Social Functioning

Social disability of bipolar patients proved to be similar to that of depressive subjects [15, 38], and the majority of these patients did not reach their premorbid level of social functioning [6, 17] so that difficulties in social functioning are concomitant to affective disorders [39–42], although they may be more marked in bipolar disorder.

After the remission of manic or depressive episodes, a recovery of premorbid function is expected. However, many authors have described a significant social disability, even in fully remitted patients [15, 43–45]. In a 12-month follow-up, after a first episode of psychotic mania, 90% of patients achieved syndromic recovery at 6 and 12 months, whereas 40% had not recovered symptomatically at 6 and 12 months, still showing anxiety or depression, whereas with respect to the functional recovery, nearly two thirds of the patients failed to return to previous levels of functioning [46].

Impairment in the social and leisure activity areas in particular has been found, showing that bipolar patients seem to have fewer social interactions with their friends than normal subjects [40, 42, 47].

<p>| Table 1. The most relevant studies on functional outcome in bipolar patients |
|-----------------------------------------------|-----------------|---------------------|---------------|</p>
<table>
<thead>
<tr>
<th>Studies</th>
<th>Number</th>
<th>Follow-up period</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrow et al. [14], 1990</td>
<td>73</td>
<td>1.7 years</td>
<td>34% had very poor global functioning; outcome was poorer for bipolar than for unipolar disorder</td>
</tr>
<tr>
<td>Tohen et al. [13], 1990</td>
<td>75</td>
<td>4 years</td>
<td>28% were unable to work; 19% could not live independently at follow-up</td>
</tr>
<tr>
<td>O’Connell et al. [130], 1991</td>
<td>248</td>
<td>1 year</td>
<td>19% had very poor psychosocial outcome</td>
</tr>
<tr>
<td>Coryell et al. [15], 1993</td>
<td>29</td>
<td>5 years</td>
<td>31% never achieved sustained recovery</td>
</tr>
<tr>
<td>Goldberg et al. [16], 1995</td>
<td>51</td>
<td>4.6 years</td>
<td>22% had poor psychosocial outcome, 14% persistent poor functioning at two follow-ups</td>
</tr>
<tr>
<td>Gitlin et al. [5], 1995</td>
<td>62</td>
<td>4.3 years</td>
<td>35% had poor occupational functioning; 61% had only fair or poor social functioning</td>
</tr>
<tr>
<td>Strakowski et al. [17], 1998</td>
<td>109</td>
<td>1 year</td>
<td>65% failed to achieve functional recovery; all subjects had prior hospitalizations</td>
</tr>
<tr>
<td>Keck et al. [18], 1998</td>
<td>134</td>
<td>1 year</td>
<td>76% failed to achieve functional recovery; patients with mixed or manic episodes at index did not differ in recovery rates at follow-up</td>
</tr>
<tr>
<td>Tohen et al. [6], 2000</td>
<td>219</td>
<td>2 years</td>
<td>63% failed to reach functional recovery</td>
</tr>
<tr>
<td>Hammen et al. [89], 2000</td>
<td>52</td>
<td>2 years</td>
<td>The variables that better predicted work adjustment were recent symptoms and number of hospitalizations</td>
</tr>
<tr>
<td>Judd et al. [4], 2002</td>
<td>146</td>
<td>12.8 years</td>
<td>Longer intake episodes and those with depression only or cycling polarity predicted greater chronicity during long-term follow-up, as did comorbid drug use disorder</td>
</tr>
<tr>
<td>Judd et al. [3], 2003</td>
<td>86</td>
<td>13.4 years</td>
<td>Poor previous social functioning predicted greater chronicity</td>
</tr>
<tr>
<td>MacQueen et al. [100], 2003</td>
<td>138</td>
<td>3 years</td>
<td>Patients with subsyndromal symptoms had lower GAF scores than euthymic patients</td>
</tr>
<tr>
<td>Tohen et al. [50], 2003</td>
<td>166</td>
<td>2–4 years</td>
<td>Only 43% achieved functional recovery</td>
</tr>
<tr>
<td>Blairy et al. [55], 2004</td>
<td>144</td>
<td>Cross-sectional</td>
<td>Bipolar patients were less adjusted than normal controls in leisure activities, relationships with extended family, marital relationships and work activities</td>
</tr>
<tr>
<td>Goldberg and Harrow [51], 2004</td>
<td>34</td>
<td>10 years</td>
<td>Half of bipolar patients showed sustained remissions or patterns of improvement, while 30–40% experienced some functional decline</td>
</tr>
<tr>
<td>Chengappa et al. [58], 2005</td>
<td>139</td>
<td>52 weeks</td>
<td>Two thirds of recovered subjects remained unemployed for pay while half received disability compensation</td>
</tr>
<tr>
<td>Judd et al. [99], 2005</td>
<td>391</td>
<td>20 years</td>
<td>Symptom severity and psychosocial disability fluctuate together during the course of illness; subsyndromal depressive symptoms are associated with significant impairment in bipolar I and II disorders, whereas subsyndromal (hypo)manic symptoms may even enhance functioning in bipolar II disorder</td>
</tr>
<tr>
<td>Conus et al. [46], 2006</td>
<td>54</td>
<td>1 year</td>
<td>61% of patients failed to return to previous level of functioning</td>
</tr>
<tr>
<td>Kebede et al. [148], 2006</td>
<td>315</td>
<td>1–4 years</td>
<td>Social and physical functioning deficits were present in 52–86 and 35–47% of recent-onset and long-standing cases, respectively</td>
</tr>
<tr>
<td>Jaeger et al. [118], 2007</td>
<td>78</td>
<td>1 year</td>
<td>This is the first study examining the predictive value of neurocognitive deficits, independent of residual mania or depression, for long-term functional recovery following hospitalization; selective neurocognitive deficits are predictive of long-term functional recovery</td>
</tr>
<tr>
<td>Tabares-Seisdedos et al. [119], 2008</td>
<td>43</td>
<td>1 year</td>
<td>Processing speed and a global neurocognitive index were the factors that best predicted functional recovery; subclinical symptoms also influenced the functioning of euthymic bipolar patients</td>
</tr>
</tbody>
</table>
Some reports indicate that social disability is sustained as long as 2 years following onset [15, 40, 48] and may be the result of residual symptoms [48, 49]. Nevertheless, we do not really know the cause-effect directionality for residual affective symptoms and low functioning. In any case, worse social functioning may also lead to more depressive symptoms [49]. In this regard, a poor social functioning predicted a shorter time to relapse [5].

Tohen et al. [6, 50] also reported full clinical recovery in 98% of patients 2–4 years after a first episode with psychotic symptoms, whereas only one third of patients achieved a complete functional recovery. Over a 10-year follow-up period, about half of bipolar patients showed sustained remissions or patterns of improvement, while 30–40% experienced some social disability [51].

Bipolar disorder seems to have a negative effect upon the patients’ quality of life, particularly in the areas of social relationships [52], although the term ‘quality of life’ reflects the patient’s subjective perception. In addition, Morgan et al. [53] showed that despite low levels of chronicity, the burden of social disablement associated with bipolar disorder is high. Comparisons with schizophrenic patients highlighted an equal or greater utilization of services by bipolar patients, suggesting that bipolar disorder is a major cause of impairment and compromised quality of life. Anyway, findings are consistent with respect to persistent impairment of social functioning over time.

In general, bipolar patients report deficits in social functioning, including interpersonal relationships, enjoyment of recreational activities and overall contentment, compared with controls.

Work Functioning

Work impairment basically refers to the impact of illness on a person’s ability to work, impairment in occupational role performance and reduced work productivity associated with output, in relation to input.

Bipolar disorder symptoms can have a negative impact on the individual, reducing health-related quality of life and functioning especially regarding employment and work productivity [54–56]. Patients with mood disorders are more likely to report declines in job status and income [15].

Less than 50% of the population with bipolar disorders report having an active job. In every country where statistics are available, the percentage of unemployed people in the bipolar disorder group (age range: 46–58 years) is significantly above the mean level of unemployment [57]. It is also above the European mean average for the percentage of the population with the same level of education. These data suggest that unemployment is generally higher among bipolar patients than among those with unipolar depression, combined with greater difficulties in the area of job retention. In addition, among those who have a full-time or part-time job, 13–34% acknowledge having frequent problems at work [57]. Other longitudinal studies have shown similar results [51, 58] (table 1). In an Australian general population survey, bipolar patients showed greater disability as measured by days out of role compared with major depressive patients [59]. In a Spanish sample, 22% of patients were actively employed and 12% were temporarily unable to work. These results clearly show the important repercussions of this illness on the patients’ employment situation and its negative impact on their quality of life [60]. In a large study by the Stanley Foundation Bipolar Network, 62% of 261 outpatients reported moderate to severe impact of the illness on occupational functioning [61].

Moreover, the baseline results of the European Mania in Bipolar Longitudinal Evaluation of Medication on the functional status of patients with mania (n = 3,497) suggested that 68% of patients showed high work impairment, moderate to severe impairment, including 21% of patients who were unable to work at all. In this study, clinicians were asked to rate the patient’s impairments in work activities in the previous year before mania [62]. Similarly, up to 67% of bipolar patients in a 6-month follow-up study showed high work impairment [10]. Moreover, as mentioned in the previous section, low work functioning may also lead to a shorter time to relapse [5].

In view of previous findings, a high rate of bipolar patients show moderate to severe disability on work functioning. The most frequent difficulties are associated with a lack of continuity in work history, job loss, illness management strategies in the workplace, stigma and interpersonal problems at work [56].

Due to the illness progression, a huge number of bipolar patients cannot return to their previous job, and they are compelled to adapt to other workplaces requiring lower capacities (e.g. an economist working as a receptionist).

Family Functioning

Some findings show that caregivers’ beliefs about the illness might predict caregiver burden, and this burden could influence the outcome of bipolar disorder. Burden studies of bipolar patients and their families are scarce, and most are descriptive, with no long-term follow-up [63].
Table 2. Factors associated with a low functioning and disability

<table>
<thead>
<tr>
<th>Sociodemographic factors</th>
<th>Clinical factors</th>
<th>Cognitive factors</th>
<th>Pharmacological factors</th>
<th>Environmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Age of onset</td>
<td>Persistent cognitive dysfunctions</td>
<td>Number of medications</td>
<td>Social support and attitudes</td>
</tr>
<tr>
<td>Male sex</td>
<td>Number of episodes</td>
<td></td>
<td>Side effects of medication</td>
<td>Family support and attitudes</td>
</tr>
<tr>
<td>Poor premorbid adjustment</td>
<td>Number of hospitalizations</td>
<td></td>
<td></td>
<td>Health services, systems and policies</td>
</tr>
<tr>
<td></td>
<td>Prior history of psychotic symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent subclinical symptoms</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Rapid cycling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychiatrist and medical comorbidities</td>
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</tr>
</tbody>
</table>

In primary care practice, patients who screened positive for bipolar disorder reported an increased disability in family life [64]. Chakrabarti and Gill [65] found that the burden of care among families of patients with affective disorders was considerable, but was greater in relatives of bipolar patients than in those of patients with unipolar depression. These authors suggested that social disruption, due to manic episodes, might explain this difference. Prolonged illness and high levels of disability among patients consistently correlated with severity of burden [66]. A study of 266 bipolar or schizoaffective patients concluded that 93% of caregivers reported at least moderate distress related to the patient’s problem behaviour, social dysfunction or the illness’s adverse effects on the caregiver’s work, social and leisure time [67]. However, in another study, compared to caregivers of patients with unipolar depression, caregivers of patients with bipolar disorder showed a significant reduction in burden 1 year after their relative had been discharged from the hospital [68].

The importance of family burden has become clearer since several authors [69, 70] reported that family burden could condition the functioning of bipolar disorder. The most troublesome aspects that increase burden, as reported by spouses of euthymic bipolar patients, were financial difficulties, unemployment, marital problems, recurrences leading to rehospitalization and social withdrawal due to the illness [55, 71]. Moreover, many first-degree relatives of patients with bipolar I disorder may also have bipolar disorder and other mood disorders, thus increasing the burden on family life and their own disability.

Subjects with bipolar disorder show a greater likelihood of being widowed, separated or divorced [59]. Those patients with mania, hypomania or subsyndromal manic symptoms had greater marital disruption compared to a group without mental disorder [72]. One important thing to be taken into consideration is, on one hand, that this illness represents an important family burden, but, on the other hand, the attitudes and support of immediate family members as well as social attitudes may also act as environmental facilitators or barriers on the functional outcome of bipolar patients [73].

**Correlates of Low Functioning in Bipolar Patients**

The factors associated with functional outcome vary between studies and have been difficult to replicate, because of different approaches and the use of differing instruments to assess functional outcome. Table 2 shows several factors associated with low functioning and disability in the literature.

**Clinical Factors**

Poor functional outcome in bipolar disorder has been associated with treatment non-compliance [74], comorbid substance abuse [75–77], anxiety disorders [78, 79], presence of mixed affective states [80, 81], psychosis [12, 82], number of past episodes [5, 16, 83, 84], rapid cycling [85, 86], history of suicidal behaviour and medical comorbidities [28, 85, 87], personality features [85, 88] and hospitalizations [17, 89–91].

In bipolar disorder, subsyndromal symptoms are very common; they interfere with functioning and quality of life, and may increase the risk of relapse. Subsyndromal symptoms, especially depressive symptoms, are positively correlated with disability in both social and occupational functioning [10, 16, 47, 49, 92–94]. Low functioning, associated with depressive symptoms such as excessive number of days spent in bed, was comparable to or worse than that typically associated with 8 chronic medical illnesses which included hypertension, diabetes and arthritis [28].

Ozer et al. [90] found that all of these measures related to quality of life, disability and overall functioning evaluated the same areas of life, e.g. social, occupational and...
vocational life. Although each of them seemed to be sensitive to different aspects of life, subthreshold depression was the strongest common factor that influenced all 3 measures.

There is evidence that many bipolar patients are symptomatic most of the time, in spite of adequate treatment [95, 96]. Subsyndromal depressive symptoms have been found to be more common than hypomanic or mixed symptoms in longitudinal studies [3, 4, 97, 98]. In a recent study, subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, were associated with significant impairment [99]. Persistent symptoms are, therefore, associated with significant morbidity and functional impairment for patients with bipolar disorder [100]. Severer symptoms of depression were predicted by an earlier age at onset of depression, 10 or more episodes of depression, a history of limited occupational functioning and a depressed mood at entry into the Stanley Foundation Bipolar Network [97, 98]. In this regard, bipolar depression is associated with considerable suffering, disability, mortality and medical morbidity [101].

Patients with bipolar disorder spend a greater amount of time in the depressed phase than the manic phase and view the depressive phase as resulting in greater psychosocial impairment or disability [102].

Disability related to bipolar depression affects many external and social aspects of patients’ lives. Episodes of depression are associated with greater impairment in work, family and social life than episodes of mania [84, 90, 102]. On the other hand, the clinical state of the illness may influence findings on functioning or on quality of life measures. Subjective quality of life in manic patients may not adequately reflect the objective functional outcome status, and this may be related to poor insight [103]. Mixed states may lead to higher levels of disability [80, 81].

With respect to bipolar subtypes, no differences were found between bipolar I and II patients followed over 5 years regarding psychosocial disability [11]. Judd et al. [99] observed that, at each level of depressive symptom severity assessed, bipolar I and bipolar II disorders are equally impairing. Interestingly, subsyndromal hypomanic symptoms appeared to enhance functioning in bipolar II patients. This highlights an important difference in psychosocial functioning between bipolar I and II patients [3]. An early onset of bipolar disorder may also influence the functional impairment [97, 98]. That is approximately one third of patients with bipolar disorder develops significant symptoms before the age of 15 years, and the prevalence in adolescence is approximately 1% [104, 105]. In children, bipolar disorder has serious adverse effects on development, social functioning and academic achievement.

Other clinical correlates of the level of functioning in bipolar patients treated in primary care settings, such as a chronic illness course, history of rapid cycling, suicidal behaviour, psychiatric comorbidity, hypothyroidism and diabetes mellitus, regardless of treatment of these conditions [85], have not been well investigated. The most common medical illnesses are cardiovascular disease, diabetes mellitus, obesity and thyroid disease. Treatment of comorbid medical conditions may reduce the risk of adverse outcomes [87]. Other authors have found that family history of affective disorder, age at intake and comorbid substance abuse predicted functional outcome at 12 months after a first episode of psychotic mania [46]. Finally, the impact of psychotic symptoms on the functioning of bipolar patients is not clear. Keck et al. [106] did not find differences between patients with and without a history of psychosis on social and work functioning. However, these authors point out that the lack of apparent prognostic impact may be related partly to the high morbidity and poor functional outcome of a substantial proportion of the total cohort.

In view of the literature review, the most consistent findings among clinical factors are related to subsyndromal depressive symptoms and comorbid conditions, especially substance abuse and anxiety disorders. More studies on other comorbidities with personality disorders or medical illnesses, for instance, are needed, since they may cause disruptions in functioning in these patients.

The Relevance of Cognitive Dysfunctions

Cognitive function has not been routinely examined in the studies of psychosocial functioning in patients with bipolar disorder because clinical variables have been thought to impact function more than cognition [107]. Traditionally, schizophrenia was considered to be highly impairing and bipolar disorder not, but now we know that the neuropsychological differences between these two conditions are subtle [108].

Patients with lower psychosocial functioning showed more generalized verbal memory deficits, even in simple tasks, indicating difficulties in encoding and retrieval of verbal information. Verbal memory impairment has been consistently suggested to be associated with work impairment in euthymic bipolar patients [34, 35, 109]. In a recent study, spontaneous verbal recovery of information was the variable that best predicted the psychosocial outcome of euthymic bipolar patients (n = 77), even after controlling for the effect of very mild depressive symp-
toms [23]. Difficulty remembering long-term information may represent a serious problem for bipolar patients in their occupational functioning as well as in their interpersonal relationships. In general, patients complain about having difficulty in remembering names and conversations both in the distant and more recent past. The measures of functioning in some of these studies were GAF scores and the work functioning of patients during the last 3 years prior to inclusion [23, 34, 35]. Therefore, verbal memory might be a good predictor of functional outcome as measured by the GAF, even in patients fulfilling strict criteria for euthymia [23, 34, 35]. After controlling for low levels of affective symptoms, the patients with difficulties retaining information had a poorer functional outcome [23, 35]. Previous publications found a relationship between verbal memory deficits and poor psychosocial functioning [110–112]. Nearly 40% of early-onset patients showed cognitive impairment in later life, and 27% also showed impaired functional outcome using the GAF [113]. Other recent reports have suggested that frontal executive impairments may also be related to low psychosocial functioning [114–117]. To date, there are only two longitudinal studies focused on cognitive functioning as predictor of functioning. Attention and verbal fluency were significantly predictive of functional recovery 12 months later [118]. The other follow-up study found that cognitive factors were the best predictors of functioning in the long term, especially executive function and processing speed measures as well as a global cognitive index [119].

Cognitive functioning involves limbic structures, such as the hippocampus, amygdala or the prefrontal system, and their interconnections are required to establish significant interpersonal relationships, in order to achieve a suitable academic or work functioning. Therefore, cognitive abilities including memory, planning or problem-solving strategies, the emotional processing of information or social cognition, for instance, are probably needed to cope satisfactorily with the different psychosocial situations or events.

Other Factors
Demographic variables, such as older age [120], male sex [121, 122] and low socio-economic status [17, 18, 123], may also be considered as variables that influence the functioning of bipolar patients, although these results have yet to be sufficiently replicated. Other aspects could be environmental factors, such as social support [9, 31, 32] or life events [33]. Moreover, there are studies showing that the problems and difficulties in functioning experienced by patients with bipolar disorder are closely related to the support provided by different agents and environmental factors, including the family and the community, social services, systems and policies [21]. Finally, within the environmental factors, support of health professionals and of family members and friends have been found to be facilitators of functioning, while attitudes of immediate family members and friends, social norms, practices and ideologies, as well as health services, systems and policies were found to be barriers identified by euthymic bipolar patients [73].

With respect to premorbid functioning, some authors have suggested that impairments in premorbid social functioning were not specific to schizophrenia and were seen also in bipolar disorder [124]. Nevertheless, Cannon et al. [125] observed that significant impairments in neuromotor, receptive language and cognitive development were present only in children later diagnosed as having schizophreniform disorder, but not in those children later diagnosed as having mania. Similarly, Reichenberg et al. [126] also found a poorer premorbid intellectual, language and behavioural functioning in schizophrenic individuals, compared to bipolar patients without psychiatric symptoms, who did not differ from healthy controls. These authors suggested that the absence of psychosis might be a good predictor of functioning.

With regard to pharmacological factors, polypharmacy may be associated with a poorer outcome, inducing rapid cycling or causing severer adverse effects, as well as affecting GAF scores [23, 85]. Nevertheless, polypharmacy is more common in patients with a severer illness course, and the underlying pathology may be associated with poor functioning such as an increased risk of side effects and interactions in polymedicated patients [97]. A study of the benefits on psychosocial functioning using different medications is needed. Some drugs appear to show several advantages with respect to the probability of being employed or paid for work [36, 127, 128]. Moreover, patients receiving lithium doses that achieved therapeutic serum levels had better psychosocial functioning than those receiving doses that achieved low serum levels [123], so probably treatment adherence plays an important role for functioning.

Conclusions
The different outcome measures, such as functioning, disability and quality of life, are somewhat overlapping concepts which interact with each other. A high percent-
age of bipolar patients, between 30 and 60%, shows significant disability in different areas of functioning including social, work and family life. Several factors may be considered correlates of functioning in bipolar disorder but have not been widely investigated, therefore it is really difficult to address some conclusions.

Functioning and Its Correlates

In spite of clinical remission, nearly half of the patients with bipolar disorder continue to experience difficulties in their functioning, including work impairment, family disturbances, marital and, in general, interpersonal difficulties. These dysfunctions may be generally moderate to severe in a high portion of patients and seem to be related to several factors, mainly clinical and cognitive ones. Nevertheless, the weight of these and other factors in the functioning of bipolar patients has not been broadly studied, compared with studies targeting schizophrenic patients. The relevance of neurocognitive factors has been underestimated, whereas most studies have emphasized the importance of clinical variables. Further research should thoroughly examine which variables may constitute the best predictors of functioning in bipolar disorder, since these variables have been partially investigated. On one hand, the most common factors associated with low functioning are related to subsyndromal states and particularly persistent subdepressive symptoms, and comorbidity, especially with anxiety disorders and alcohol abuse, but other comorbid conditions could also be involved. With respect to other clinical factors, such as depressive episodes, psychotic symptoms, the number of episodes, the duration of illness or an earlier age of onset, the results from different studies seem to be less conclusive. On the other hand, the role of cognitive impairment in low functioning appears to be increasingly relevant, although further research is needed to confirm its true impact, particularly on the ‘softer’ side of the bipolar spectrum [129]. Finally, other factors, such as medication, low socio-economic status, poor social support or poor premorbid adjustment, may also be associated with the functional impairment of bipolar patients, but their impact requires further research.

The relationship between residual affective symptoms, neurocognitive impairment and psychosocial disability has strong implications regarding the long-term management of bipolar disorders. These factors may increase the risk of low functioning and disability in bipolar patients. However, up to date, the lack of research focused on the relationship among clinical factors, cognition and functional outcome does not allow conclusions with respect to the differential weight of the distinct factors in bipolar disorder. Probably, the recent findings suggest that the relationship between cognitive impairment and low functioning should be examined independently of clinical and demographic variables in clinically stable patients.

Limitations of the Studies

The main limitations are the scarcity of studies on euthymia or the use of heterogeneous samples including patients in different states, which rarely control for the effect of subsyndromal symptoms. Other reports do not differ between unipolar and bipolar patients. Most studies are cross-sectional. Different instruments are used to assess functioning or disability, which usually do not allow to compare results, and generally are not specific for bipolar disorder. Perhaps, one of the most important problems is the lack of uniformity and specificity of diagnosis and assessment, as well as little standardization of the instruments.

Therapeutic Implications

Until recently, treatments had been focused on clinical remission; however, target or response criteria should also include the achievement of complete functional recovery. Despite the treatment effectiveness associated with lithium, mood stabilizers and psychosocial interventions, recent longitudinal studies have shown substantial relapse rates, residual symptoms and impairment in functioning [5, 14–16, 130, 131].

Current treatment strategies show clear limitations regarding their capacity to improve the functioning and reduce the disability of bipolar patients. As many as 44% of a sample of euthymic patients followed up at a specialized programme for bipolar disorders had a poor functional outcome [23]. This low functioning, even in treated euthymic patients, is one of the main factors explaining why bipolar disorders have been ranked seventh amongst the worldwide causes of non-fatal disease burden, as measured in disability-adjusted life years [2]. Moreover, it is consistent with recent studies highlighting the social and economic burden of bipolar disorder and the modest impact of available interventions on the functional outcomes of a large proportion of patients [132], so further research should be addressed to this issue.

Psychoeducation and other psychosocial approaches for bipolar disorder are known to generally improve the outcome of illness [133–135], and it has been reported that interventions that focus on treatment adherence may yield positive results in this specific area [30, 133, 136–138]. Overall social functioning measurements and em-
ployment rates were also significantly improved with psychoeducation [139]. Increased emphasis on psychoeducation and cognitive modification of behavioural patterns in the management of this disorder with combined psychological and pharmacological tools would be helpful [140]. Psychosocial rehabilitation may be useful in bipolar patients who do not achieve complete functional recovery [141]. An important efficacy-effectiveness gap further compromises the translation of the evidence based on bipolar disorder treatment into clinical practice [142]. The whole bipolar spectrum should be taken into account in the study of functioning and disability, since not only bipolar I patients appear to show difficulties, but also bipolar II and probably cyclothymic patients [143, 144].

Family burden also seems to influence the outcome of bipolar patients, so the effect of family intervention on the burden of caregivers should be investigated, especially when threat and coping appraisals have been related to the experience [67]. Further longitudinal studies are needed to address the burden experienced by caregivers, identify factors related to this burden, and analyse the relationship between family burden and bipolar disorder outcome. Further research should study the effect of family interventions on the burden experienced by caregivers, and its impact on the patient’s outcome [63]. These interventions may influence some environmental factors, such as family support and attitudes that may act as facilitators or barriers in functioning.

Finally, if neurocognitive factors, such as verbal memory impairment and probably some frontal executive dysfunctions, are good predictors of psychosocial functioning, cognitive rehabilitation strategies should also be included in the treatment of patients who show these persistent cognitive dysfunctions [145].

Bipolar disorder is often undiagnosed or misdiagnosed in the general population, leading to undertreatment and continuing disability. The combination of pharmacological and psychological approaches is essential to maximize patient response, taking into account not only the clinical response, but also the social and occupational functioning of bipolar patients [146]. Experts should shift the treatment focus progressively from symptom improvement to full recovery, which includes symptomatic and functional recovery [96]. Furthermore, the introduction of newer drugs having better tolerability profiles together with psychosocial strategies or programmes may have a positive impact on cognitive, social and occupational functioning. Therefore, a multidisciplinary approach to the management of bipolar disorder, integrating pharmacotherapy and psychosocial interventions, may enhance long-term patient outcomes, such as stability or euthymia, and improve occupational and/or social functioning, as well as treating comorbidities and other causes of long-term disability.

The development and use of specific instruments to assess functioning and disability in these patients should be one of the main goals to be achieved in further research, as well as the creation of core sets for bipolar illness [21]. There is, however, little standardization in the use of these instruments, and therefore comparisons among studies are difficult or impossible. In addition, these instruments typically cover only selected aspects of the entire experience associated with bipolar disorder. It is also important to note that there is no condition-specific instrument for bipolar disorder; the instruments cited above were not developed to measure the problems specifically associated with bipolar disorder [21], mentioned briefly as limitations. Moreover, there is a need of practical, short and user-friendly scales that are sensitive to change, to be included in clinical trials for going beyond just the clinical response towards functional recovery. Such instruments are currently being developed, such as the Functioning Assessment Short Test [147].

According to the conclusions of this extensive review, bipolar patients, regardless of their clinical state, show impairments in the work, social and family functional areas. Several factors are associated with low functioning and disability; the most frequent among clinical factors are persistent subsyndromal symptoms and the neurocognitive factors are progressively considered as having a negative impact on the functional outcome. Therapeutic strategies are needed to improve not only the full clinical, but also the functional recovery of bipolar patients.

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