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Review article

The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment

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ABSTRACT

Background: Most longitudinal or treatment studies in bipolar disorder have used symptomatic or syndromal status as the primary outcome variable. More recently, psychosocial functioning has been highlighted as a key domain of outcome. Patients with bipolar disorder appear to be impaired in all functional domains, although the factors that cause impairment have not been clearly specified.

Methods: This paper reviews cross-sectional and longitudinal studies on functional impairment and its relationship to symptomatic, neurocognitive, personality, and stress variables in bipolar disorder; and the implications of these relationships for defining treatment targets. 93 articles were located through comprehensive MEDLINE, SCOPUS and Web of Science searches.

Results and discussion: Functional recovery following a mood episode consistently lags behind symptomatic and syndromal recovery. Longer term functional impairment is only partly explained by the number of manic/hypomanic episodes. Depression (including subsyndromal states) and persistent neurocognitive impairment are the strongest correlates of functional impairment in bipolar disorder, with personality and psychosocial stressors playing secondary roles. Possible treatment options include: more aggressive treatment of subthreshold depressive states, pharmacotherapies that target cognition (e.g., stimulants), and adjunctive psychotherapies including cognitive remediation.

1. Introduction

The natural history of bipolar disorder is characterized by frequent and recurrent mood episodes. Since Kraepelin's seminal studies distinguishing manic depressive insanity (bipolar disorder) from dementia praecox (schizophrenia) (Kraepelin, 1921), it has been clear that the natural history of bipolar disorder is characterized by recurrent episodes. Despite the evolution of multiple effective mood stabilizers that prevent manias, depressions or both (Gitlin and Frye, 2012), naturalistic studies repeatedly demonstrate breakthrough episodes of mania or depression with relapse rates over 1–4 years in *treated* groups ranging from 40% to 60%, and 4–5 year relapse rates range from 60% to 85% (Goodwin and Jamison, 2007; Gignac et al., 2015).

Additionally, modern studies have documented moderate to severe functional impairment associated with bipolar disorder in any and all domains evaluated (Coryell et al., 1993; MacQueen et al., 2001; Keck, 2006; Judd et al., 2008; Sanchez-Moreno et al., 2009; Wingo et al., 2009). Bipolar I and II patients still have significant functional impairment after statistically controlling for the concurrent level of depression (Sanchez-Moreno et al., 2009; Coryell et al., 1989; Judd et al., 2005; Ruggero et al., 2007). Highlighting the importance of functional vs. syndromal outcomes, it has been estimated that 79% of the societal cost of bipolar disorder is due to indirect costs such as occupational impairment as opposed to direct treatment costs such as hospitalization (Dilsaver, 2011). In fact, BD is the fifth leading cause among psychiatric disorders of lost years of work (Ferrari et al., 2016).

The two methods of measuring outcome- symptomatic/syndromal vs. functional - highlight a number of questions that will be addressed in this review:

1. What is measured by these different outcome variables?
2. What are the relationships between syndromal or subsyndromal symptoms and different types of functional outcome in bipolar disorder?
3. What are the non-symptomatic (e.g., neurocognitive) correlates of functional outcome?
4. Finally, what are the implications of these findings for the pharmacological or psychosocial management of bipolar disorder?

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[1] Both authors contributed to the literature review and writing of this article. They have both approved the final article.

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2. Methods

2.1. Studies were identified through MEDLINE, SCOPUS, and Web of Science

The search terms included blocks pertaining to bipolar disorder (bipolar, mania, depression, hypomania, manic-depression) and functioning (impairment, psychosocial, occupational, disability, work, cognition, neurocognition, stress, remediation). The searches were limited to the period between Jan. 1, 1980 and Sept. 1, 2016. We also screened articles cited in existing reviews of the literature on functional outcomes, stress, and psychosocial interventions (Andreou and Bozikas, 2013; Cardenas et al., 2016; Cullen et al., 2016; Levy and Manove, 2012; Miklowitz and Johnson, 2009a; Salcedo et al., 2016).

This article addresses some of the same topics covered in earlier reviews (e.g., Andreou and Bozikas, 2013; Levy and Manove, 2012). However, we also address several issues that had not been fully investigated previously: the effects of subsyndromal symptoms on functional impairment, either in conjunction with or independent of neurocognitive factors; the influence of personality traits on social-occupational functioning; new pharmacological strategies (e.g., non-dopaminergic stimulants); and new psychosocial methods (e.g., functional remediation) for treating functional disability associated with bipolar disorder or its comorbid disorders.

We screened 2418 peer-reviewed articles for eligibility. Eligibility was based on direct relevance of the article to (1) the prevalence or extent of functional impairment in bipolar disorder (accounting for 278 citations), (2) the roles of symptoms and neurocognition (611 citations); (3) the roles of comorbid disorders or personality variables in functional impairment (663 citations); and (4) treatment studies or clinical position papers (866 citations). After excluding duplicate citations or papers that did not address these questions, we selected 93 articles for inclusion.

2.2. Measuring outcome in bipolar disorder

Psychopharmacological studies typically measure outcome by counting the number of and severity of symptoms, or (for maintenance trials), computing time to relapse or recurrence. A variation on the theme of symptom-based measurement is constructing cumulative measures of symptoms, similar to the area under the curve in which the relevant unit of measurement is symptom severity over time. Cumulative measures of depression equate, for example, six months of mild depression with three months of more severe depression. Cumulative measures of psychopathology taking into account symptom severity and time provide a somewhat richer and more accurate picture of a patient's course compared to simply measuring relapse rates or survival curves, and may be more strongly correlated with functional outcome measures than are symptom measures from a single time point (Gitlin et al., 1995).

2.3. Functional outcome and its measurement

Focusing solely on the evolution of symptoms as the only outcome may falsely estimate the “success” of a treatment. As an example, treating a patient to symptomatic recovery (i.e., prolonged euthymia) but not functional recovery (i.e., working at full capacity, having strong interpersonal supports and reporting a high quality of life) would be considered a successful treatment in a study focusing only on symptomatic outcomes.

These limitations in symptom-based outcome definitions have given rise to efforts in measuring functional outcomes – the degree of success of patients' lives. A variety of reliable measures of functioning in bipolar disorder exist (e.g. Rosa et al., 2007) but none has achieved the type of acceptance comparable to that of the Hamilton Depression Rating Scale (Hamilton, 1960) or the Young Mania Rating Scale (Young et al., 1978). Although some studies use the single dimensional Global Assessment of Functioning Scale (Endicott et al., 1976), most functioning scales assess at least two domains- role function and social function- with some assessing recreation or life satisfaction. Role function includes the relative ability to handle work, school or household roles, allowing patients in different social contexts to be compared in a crude way. Social functioning may include romantic relationships, interactions with family members or friendships.

Since the available scales may differ substantially in what is measured, and few studies include more than one functioning measure, the results across studies may differ based on measurement variance as opposed to outcomes. Some studies use self-report measures of functioning whereas others use observer-based measures. Thus, in one study functioning may the reflect patients' assessment of their progress relative to other phases of one's life, whereas in another study functioning may mean relative to other patients.

A less frequently used outcome measure is ‘quality of life’ (QOL) which measures whether individuals feel satisfied or fulfilled. Compared to both symptom based or function based measurements, quality of life is more subjective since the former evaluate individuals according to an objective (if culturally determined) standard, whereas QOL is entirely based on the individuals' subjective appraisal. Given the inherent subjectivity in its definition, there is no consensus on the optimal rating scales to use in measuring QOL, although reliable measures have been proposed (e.g., Michalak et al., 2005). Additionally, mood states, especially depression, are likely to affect functioning and especially, QOL measures. Therefore, QOL measures need to be obtained during euthymic as well as symptomatic periods to avoid simply measuring the cognitive distortions associated with mood states.

Overall, bipolar patients score lower than control populations on QOL measures (Michalak et al., 2005). This is especially so in those who are evaluated while depressed. Perhaps counterintuitively, manic/hypomanic patients also rate their QOL as lower than controls; whether this group difference reflects the common admixture of depressive symptoms within manic states, or the recognition that one's life is impaired despite current feelings of elation or heightened energy, is not clear (Michalak et al., 2005).

2.4. Relationships between functional and syndromal outcomes in bipolar disorder

It is generally assumed that a prime determinant of functional outcome is symptomatic outcome (see Fig. 1): patients who are more symptomatic, who have.

more episodes, worse episodes, and more hospitalizations will have poorer functional outcome compared to those with more benign symptomatic courses. In general, this assumption is correct. Yet, as has been repeatedly noted (MacQueen et al., 2001), a large percentage of bipolar patients who have become asymptomatic continue to be functionally impaired. In an early and dramatic example of this, six months after a hospitalization for mania, 84% of patients were syndromally recovered while only 30% had achieved their premorbid levels of function (Tohen et al., 2000). Two year follow-up data on the same cohort showed 98% syndromal remission (i.e., full symptom remission) in contrast to a 38% return to premorbid psychosocial function. These findings are consistent with subsequent studies (Conus et al., 2006, Bonnín et al., 2010, Rosa et al., 2011). Additionally, the relationship between syndromal and functional outcome may not be linear or unidirectional. Low functional status predicts a shorter time to a new mood episode (Gitlin et al., 1995; Weinstock and Miller, 2008).

Mood symptoms are inherently cyclical in bipolar disorder, but the ups and downs of the illness are not always accompanied by predictable changes in functioning. Functioning during a depressive episode may