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Review Article

Public health significance of bipolar disorder: implications for early intervention and prevention

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Objectives: Early intervention and preventive strategies have become major targets of research and service development in psychiatry over the last few years. Compared to schizophrenia, bipolar disorder (BD) has received limited attention in this regard. In this paper, we review the available literature in order to explore the public health significance of BD and the extent to which this may justify the development of early intervention strategies for this disorder.

Methods: The main computerized psychiatric literature databases were accessed. This included Medline and PsychInfo, using the following keywords: *bipolar*, *early intervention*, *staging model*, *burden*, *caregiver*, *public health*, and *manic depression*.

Results: BD is often recurrent and has an impact that goes well beyond symptomatic pathology. The burden it incurs is linked not only to its cardinal clinical features, but also to cognitive dysfunction, poor functional outcome, poor physical health, high rate of comorbidities, and suicide. At a societal level, BD induces enormous direct and indirect costs and has a major impact on caregivers. The available literature reveals a usually long delay between illness onset and the start of treatment, and the absence of specific guidelines for the treatment of the early phase of BD.

Conclusions: Considering the major impact of BD on patients and society, there is an urgent need for the development of early intervention strategies aimed at earlier detection and more specific treatment of the early phase of the disorder.

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Bipolar disorder (BD) is a common mood disorder with considerable complexities involved in its diagnosis and treatment. Although estimating its prevalence is beset with complications (1), a lifetime prevalence ranging between 0.8% and 1.6% has been suggested (2–5). When considering the broader concept of bipolar spectrum disorders, this prevalence is, however, considerably higher, ranging from 2.8% to 6.5% (6). Although its most characteristic features are recurrent episodes of mania and depression, the majority of patients with BD display a more complex clinical presentation, often associated with significant comorbidity. In addition, despite early clinical descriptions suggesting a generally good outcome (7), most patients actually suffer from significant and enduring impairments in social and occupational functioning (8, 9). All these elements explain why data from the World Health Organization's Global Burden of Disease Study (GBD) have shown that BD is the 12th leading cause of lost years of healthy life and was recently ranked as having the fourth largest global burden of disease in people aged 10–25 years (10). Moreover, the impact of the disorder is not restricted to patients themselves, and when other characteristics such as

burden on relatives and economic impact on society are taken into account, the public health significance of this disorder becomes immense.

In this context, it seems imperative to look for new treatment strategies, and among recent developments in psychiatry, the concepts of early intervention applied to psychotic disorders (including psychotic mood disorders) over the last 20 years look promising. However, the development of early intervention in the full spectrum of BD has received only limited attention until recently (11). The present paper is not intended as a comprehensive review of the BD literature, but will instead focus on: (i) reviewing the various dimensions of BD which contribute to the major burden it places on patients and society; (ii) discussing characteristics that would justify the development of early intervention strategies in BD; and (iii) identifying therapeutic targets that may allow such developments to be implemented.

Impact of BD: the multiple facets of a complex disorder

Psychopathological dimensions

Until recently, the perception of outcome in BD was restricted to remission of symptoms associated with manic episodes. In this narrow context, the disorder was considered to be characterized by its cyclical nature, full recovery between acute episodes, and broadly favorable outcome. Indeed, an important body of literature reported that resolution of the manic syndrome occurs in the vast majority of patients. For example, Dion et al. (12) studied a cohort of 44 first- and multi-episode patients with BD followed up for six months after discharge from hospital, and showed that 80% of them were symptom free, reflecting the efficacy of medication in controlling acute manic symptoms. Similar observations have been made in populations of first-episode manic patients, in whom the extent of remission of the manic syndrome ranged between 85% and 90% within six months of the index episode (11, 13).

However, although the manic syndrome is an important aspect of the disorder, it represents only one aspect, and neglects important elements that may contribute to impairment of patient suffering from this illness. Indeed, despite remission of manic symptoms in the vast majority of cases, it has been outlined that symptom-free periods are actually rare. In a recent literature review, Bauer et al. (14) showed that subsyndromal mood symptoms are frequently reported by patients receiving maintenance therapy and are associated with poor functioning. In addition, other psychopathological dimensions are often observed in patients: in a study in first-episode mania patients (13), it was found that, although 90% had reached syndromal recovery after six months, 40% had not reached symptomatic recovery, mainly due to persistence of anxiety and depressive symptoms. Recurrent depressive symptoms specifically can be a major source of morbidity in BD and can produce great suffering, impairment, and risk of suicide. An important study by Joffe et al. (15) found that participants with BD experienced depressive symptoms for 40.9% of the time during a follow-up period of almost three years. A prospective study by Judd et al. (16) cited similar figures, with their 146 participants with BD reporting mixed or depressive symptoms for almost 38% of the time in their 13-year follow-up. When these elements are taken into account, it is likely that patients with BD spend considerably less time in a euthymic state than was previously estimated.

Beyond psychopathology

Manifestations of BD go beyond symptomatic psychopathology and include other dimensions such as cognition. Although the impact of cognitive dysfunction on outcome has long been established in schizophrenia, cognitive impairment was until recently considered to be restricted to the acute phase of BD, with a diffuse pattern of cognitive impairment during manic phases (17, 18) that would fully recover between acute episodes. More recent research has shown that some degree of cognitive impairment persists in a large percentage of patients with BD (19–26) across all its phases, and specifically impacts on verbal memory, attentional processing, and executive function (27). Importantly, such cognitive dysfunction correlates with poorer occupational and functional outcome (28–30) and can be observed as early as after the first manic episode (31).

As noted above, the complexity of the treatment of BD is also linked to the fact that a significant proportion of patients present with comorbid diagnoses. Notably, the presence of these comorbid disorders at first admission suggests that they are not simply a consequence of long-term illness. The prevalence of psychiatric comorbidity ranges from 35% to 71% (11) in first-episode patients with BD, and data from Tohen et al. (32) suggest that this proportion is higher for mixed first-episode (60%) than for pure manic episodes (27.2%). In addition, 25–56% of the patients present with multi-psychiatric comorbidities (11), the two most common being alcohol abuse or dependence (diagnosed in

24–39% of the patients), and drug abuse or dependence (diagnosed in 16–35%). Other comorbid psychiatric diagnoses observed more frequently in BD than in the general population are obsessive compulsive disorder (8–13%), anxiety disorders (15–18%), impulse control disorder (23–24%), posttraumatic stress disorder (1.7–18.0%), panic disorder (6.6–8.0%), and phobic disorders (4.0–6.6%).

Finally, the risk of suicide among patients with BD is high, with reported rates of suicide attempts ranging between 25% and 50% (33, 34). Pompili et al. (35) reported that 29% of patients with BD attempt suicide at least once in their life, and data stemming from epidemiological studies suggest that patients with BD are 20 times more likely than the general population to die from suicide. Some reports suggest that 10–20% of patients with BD take their own life (36, 37).

Physical health

Unfortunately, patients with BD do not only suffer from psychiatric difficulties and functional deterioration, they also display poorer physical health than the general population. It has been shown that 32.4% of adults with BD had one or more general medical condition (38). In particular, the prevalence of obesity is increased in patients with BD (odds ratio = 1.65) (39), and two recent papers converge to show that patients with BD have a significantly higher risk than the general population for developing a metabolic syndrome, mediated both by iatrogenic and non-iatrogenic factors (40, 41). Globally, life expectancy in such patients is reduced by 13.6 years for men and 12.1 years for women (42). This reduction of life expectancy seems to result more from physical diseases and medical conditions than from external causes. In addition, Perron et al. (38) have also shown that general medical conditions are associated with significant impairments in health and psychosocial functioning.

Functional outcome in BD

As mentioned above, the main focus of outcome studies in BD has traditionally been remission of the manic syndrome, but Tsuang et al. (43) were among the first to broaden outcome criteria, by reporting that 24% of patients failed to return to work up to 30 years after a first manic episode. Dion et al. (12) made similar observations when they found that, although 80% of patients had no manic symptoms six months after hospitalization for a manic episode, only 43% had a job, and only 21% worked at their level of premorbid competence. This discrepancy between syndromal and functional outcome has since been reported in numerous studies (11, 13), and a review paper by MacQueen et al. (9) reported that between 30% and 60% of patients with BD failed to regain full functioning in occupational and social domains. Of similar concern, a number of papers have shown that the broader concept of quality of life is decreased among patients suffering from BD (44, 45). In addition, patients with BD are more likely to be single and to live in isolation, with divorce rates being reported as three to six times more common in patients with BD as in the psychiatric and general populations (46).

Considering that about 98% of people who develop BD do so before age 25 (47), a critical time in our psychosocial, academic, and occupational development, BD is likely to have a major impact on capacity to work. As mentioned above, occupational functioning in such individuals is significantly lower than in the normal population, with estimates of 30–60% of patients with BD having no paid employment (4). Among patients with BD who do have paid employment, productivity appears to be compromised. In a recent study, McMorris et al. (48) found that workers with BD had lower levels of work productivity, were more likely to miss work, have reduced working hours due to medical or mental health issues, receive disability payments, be insured or covered by Medicare, and to have been fired or laid off. This impact was similar across genders, which is not the case for depression, where work capacity is reduced to a greater extent in females. These results are similar to those reported by Dean et al. (44), who found that measures of work impairment in patients with BD were worse than those among patients with depression and similar to those among patients with schizophrenia, with high rates of work impairment, unemployment, absenteeism, and failure to return to work following an acute episode.

Financial and societal impact of BD

Taken together, all these elements have a considerable impact on the primary and secondary healthcare sector as well as on other parts of society. Although it is hard to estimate the real costs incurred by this disorder because of its likely under-diagnosis, Das Gupta and Guest (49) estimated the global annual costs of BD in the UK. In their survey they estimated costs including: (i) the management of BD from a National Health Service (NHS) perspective; (ii) management costs

borne by other statutory agencies such as local authorities; and (iii) indirect annual costs to society. Costs linked to the medical management of the disorder included general practitioner (GP) consultations, GP-prescribed drugs, GP-initiated tests (e.g., blood drug levels and biochemistry), inpatient episodes, outpatient and ward attendances, community mental health team contacts, day hospital attendances, and care in special hospitals. To these were added costs of residential care, and non-NHS day care attendances. Indirect societal costs were composed of excess unemployment, absenteeism from work, suicide, and costs linked to caregivers (e.g., caregivers' unemployment rates).

The total annual costs in the UK attributable to BD at 1999/2000 prices, based on an estimated 297,000 people with the disorder, was £2 billion, of which 10% was attributable to NHS resources, 4% to non-healthcare resources, and 86% to indirect costs. Begley et al. (47) have also reported the financial cost of BD, calculating that the lifetime cost of BD in the United States is US$24 billion, with costs ranging from US$11,720 for a person experiencing a single manic episode to US$624,785 for an individual experiencing multiple episodes.

The impact of BD on society is clearly not limited to financial costs, and similarly to the observations in other mental illness, the impact on caregivers should not be neglected. Steele et al. (50) have found that the caregivers of patients with BD present with significantly more psychiatric symptoms (including depression and anxiety) and increased use of mental health services compared with the general population. In a recent qualitative study, Bauer et al. (51) found that caregivers described non-compliance with treatment and perceived helplessness in improving depressive and manic symptoms as being the main burden. Further reported concerns were, for female caregivers, the quality of the relationship with the ill relative, and, for male caregivers, constraints on their own autonomy. These observations highlight the importance of including an evaluation of caregivers' reactions when estimating illness burden, and also emphasize the need to take caregivers' coping into account when undertaking psycho-educational and multifamily sessions.

Considering the impact of BD on many aspects of patients' lives, and accounting for its burden and cost to society, it is imperative to design strategies that improve this situation. Among potential avenues for improvement, we may be able to learn from early intervention strategies that were developed primarily for non-affective psychoses, as this research appears to be considerably more advanced than that currently existing for BD (11). The concept of early intervention potentially benefitting people with BD was noted some time ago by Goodwin and Jamison (52), who stated that: 'although illness precursors can be difficult to distinguish from the normal storminess of adolescence, it is important to do so because there is reason to believe that aggressive early treatment of manic-depressive disorder can diminish later morbidity' (52, p. 129). We will explore this concept in the following section of this paper.

Is early intervention justified in BD?

Early intervention in psychosis defines two main objectives: (i) reducing the delay between illness onset and the initiation of treatment, through the early detection and engagement of new patients, and, where possible, the detection of high-risk individuals in order to provide preventive treatment; and (ii) providing specific management for this early phase of the illness. Some results stemming from the clinical literature suggest that these objectives may also be relevant to BD.

Treatment delay in BD

Various studies on BD converge to show that the delay between the onset of the illness and the time when adequate levels of care are given is excessive (53–56). Post et al. found an 'average of 10 years between first symptoms meeting diagnostic threshold and first treatment' (56, p. 317), with Baethege et al. (53) reporting a similar average mean latency of 9.3 years between first medical contact for the mood disorder and the commencement of treatment with a mood stabilizer.

Causes of diagnostic delay in BD

Many factors can contribute to this delay in diagnosing BD. First, in the majority of cases, the index episode of illness is depression and, considering the absence of valid criteria to differentiate unipolar from bipolar depression, the most common initial diagnosis is of unipolar depression (57). Second, the clinical presentation of mania is often atypical in young patients. Specifically, young people have higher rates of mixed episodes, psychotic symptoms, and comorbidity, the presence of irritability, and flight of ideas rather than the more typical euphoria and grandiosity found in older patients. As a result, many professionals fail to diagnose mania (58). Third, hypomania can often be pleasant and induce only limited impairment, and may therefore not be spontaneously mentioned by patients in clinical interviews (59). Fourth, the

presence of substance abuse comorbidity may deflect diagnostic attention and lead to misdiagnosis (59). Finally, delay may also be linked to patients' reluctance to seek psychiatric treatment. For example, Ten Have et al. (60), in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) study on BD, observed that only four out of ten patients with BD had contacted mental health services in order to receive care. In addition, similar to the earlier findings by Lish et al. (57), Ten Have et al.'s data showed that those who established contact with mental health services rarely reported complaints related to their BD.

Consequences of diagnostic delay in BD

Many researchers have explored the impact of diagnostic delay in BD. Findings suggest that failure to identify BD early not only has clinical consequences, but can also impact on treatment response, quality of life, global outcome, and economic costs, with some of these aspects potentially being driven by neurobiological modifications that progress with illness development. We will now describe some of these in more detail.

Clinical consequences. First, considering the high rate of suicide attempts mentioned above, a prolonged phase of untreated illness puts patients at higher risk of self-harm (6). Second, there are data suggesting that delayed intervention may contribute to the development of substance abuse comorbidity in patients with BD. Geller et al. (61) have found that the age at onset of bipolar II disorder in a sample of adolescents was 11.1 $\pm$ 3.6 years, and at onset of substance dependency disorder was 15.3 $\pm$ 1.3 years, suggesting that early intervention in BD may reduce the risk of subsequent development of comorbid substance abuse. This appears to have face validity in terms of patients reporting 'self-medication' of depressive or manic symptoms by illicit substances. Third, higher numbers of manic and depressive episodes are associated with a shortening of the cycle and increased rate of relapse (62–64). Fourth, untreated illness may interfere with the attainment of age-specific social, psychological, and educational developmental goals. Specifically, most researchers have found that a delay in treatment is linked to poorer social adjustment, lower rates of employment (44), higher numbers of hospitalizations (65), forensic complications, and global impairment of the ability to complete developmental tasks (10).

Consequences for treatment. Failure to identify manic or hypomanic episodes in a patient's history may lead, during depressive phases, to the prescription of antidepressants, and to the secondary induction of rapid cycling, mania, mixed states, and treatment resistance (66). In addition, although somewhat controversial (53, 67), it has been suggested that the effect of lithium may be reduced with increasing delay between onset of the disorder and the initiation of medication (56). Moreover, misdiagnosis may also lead to inadequate psycho-education and inappropriate medication regimens likely to result in higher relapse rates, which in turn contribute to increased costs. In a recent 21-month prospective follow-up study of 792 patients with BD, Hong et al. (68) found that direct costs (relating mainly to inpatient admissions) were approximately double for patients who relapsed. Earlier diagnosis would allow earlier introduction of mood stabilizing medication and initiation of relapse prevention interventions.

Potential neurobiological implications. As mentioned above, it has been observed that there is a reduced interval between each acute episode and a shortening of cycles in patients with BD. This may be linked to the neuro-sensitization phenomenon proposed by Post et al. (69); this suggests that an increasing number of relapses produces not only acute modifications, but also more permanent alterations in neuronal activity, which is possibly transduced at the level of gene expression. These alterations, in turn, might induce a higher tendency to relapse, and possibly a poorer response to medication.

More recently, Berk et al. (70) explored the concept of neuro-progression in BD, based on the observation of this shortening of the inter-episode interval and decreased probability of treatment response over time (71). They have suggested that this stage-related variation in response to treatment is reflected by progressive neuroanatomical changes as well as by cognitive decline. They suggested further that this may relate to a number of biochemical processes which, once better identified, may become tangible targets for neuroprotection and therefore more focused treatment strategies. In this concept, the identification of discrete stages according to progression of the disorder would create a framework allowing a better understanding of pathogenesis, and the development of prevention-oriented interventions (72).

Lack of specific treatment

Besides a reduction in the delay between the onset of illness and treatment initiation, early

intervention also aims to provide specific management strategies for this early phase of the disorder. For example, it is now established that, in early non-affective psychosis, lower doses of antipsychotic medication have a similar efficacy to the doses usually prescribed to patients with long-standing disease, but are associated with a significantly lower risk of side effects (73, 74). Additionally, psychological treatment programs must be geared not only towards the phase of illness, but also the stage of psychosocial development and its associated needs and difficulties, in order to improve outcome (75, 76). Recent data suggest that this applies equally to BD, and that the efficacy of treatment varies with the stage of the disorder, response being better in the early phase. Swann et al. (77) demonstrated that the response to lithium decreases as the number of previous episodes increases, and in pooled data from mania, depression, and maintenance studies, Berk et al. (70) reported a similar decrease in the response to olanzapine as the number of previous episodes increased. While these elements suggest the need for a specific approach to drug treatment in the early phase of BD, the lack of studies focusing on the treatment of first episode mania should be mentioned. In particular, there are no data regarding the ideal duration of prophylaxis after a first manic episode or the efficacy of atypical antipsychotic agents in relapse prevention, and research is needed in this domain (78), considering that intervention should not only happen earlier, but also be effective and evidence based.

There is some debate regarding early psychological interventions, with Lam et al. (79) reporting no evidence that the phase of the disorder impacted on their effectiveness. However, large randomized, controlled trials by Scott et al. (80) and by Colom (81) indicated that cognitive behavioral therapy and psycho-educational approaches were more effective when delivered early in the course of the disorder. Smaller studies by Jones et al. (82) and Macneil et al. (75) also indicated the efficacy and acceptability of modified cognitive behavioral therapy for early intervention in BD.

Defining targets for early intervention in BD

Considering the elements described in the previous section, it seems clear that the development of early intervention strategies for BD would be justified. However, one of the prerequisites for such developments is to formulate an adequate definition of the various stages of the disorder, ranging from vulnerability to the disorder, to the initial onset phase, to persisting, unremitting symptomatic BD. In BD, both the nature of the disorder and its cyclical aspects make this task complex. First, the initial manifestations of BD range from depressive episodes of varying intensity to mania of abrupt onset, both of which can be hard to diagnose (59). In many other cases, onset may be considerably less clear-cut and stem from ill-defined mood disturbances which can start early in life and later build into a first manic or depressive episode. Even though such 'attenuated' symptoms can be identified, their specificity is low and they may be hard to distinguish from manifestations of early adolescence, normal reactions to life events, or early signs of other disorders. In addition, when including the entire spectrum of BD, the definition of sub-threshold manifestations becomes even more complex.

In this context, before early intervention strategies can be implemented, additional work needs to be done in order to better define the three following potential targets: (i) developing a better characterization of the specific and unique elements of bipolar depression, allowing prospective identification of bipolarity in individuals presenting initially with depression; (ii) gathering more extensive knowledge about initial manic manifestations of the disorder; and (iii) exploring and defining the more progressive forms of onset which, by analogy with early psychosis, could be defined as the *initial prodrome* to BD (83–86). This may or may not be possible. The initial manic episode may be difficult to clearly distinguish much in advance from the risk of a broader initial psychotic episode. The competing models are of early sub-threshold specificity which has yet to be demonstrated and a more pluripotent model for serious mental illness. The clinical staging framework has been constructed as a heuristic strategy to explore these alternative pathways (70, 72). It therefore remains to be seen to what extent it might be possible to implement specific treatment strategies adapted to patients' needs, to explore the neurobiological mechanisms involved in the various stages of the disorder, and to improve our understanding of the nature of BD. An alternative scenario would be that cross-diagnostic neuroprotective and psycho-protective strategies might be applicable and effective. In either case, we can aim for the development of novel treatment approaches of higher efficacy.

Conclusions

BD can clearly have a significant impact at an individual, family, and societal level. There is growing evidence that, when looking beyond simple symptomatic recovery from mania, outcomes may not be as positive for individuals with BD as was

previously reported. Specifically, recent research has highlighted poor functional recovery relating to ongoing depressive symptomatology and possible cognitive difficulties. Early intervention appears to offer significant promise, both in terms of reducing secondary morbidity and in achieving better symptomatic recovery. It appears that there may be much to be learned from the literature and from research on early intervention in non-affective psychosis, which has been studied for significantly longer than that for BD. We recognize that there is still considerable work to be done, specifically in clarifying the staging model for BD and in measuring the effectiveness of specific biological and psychosocial interventions at various phases of the disorder. However, it is perhaps through this that we will be able to obtain better outcomes for patients with BD.

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