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## EDITORIAL

### Beyond psychosis: The challenge of early intervention in bipolar disorders<sup>☆</sup>

### Más allá de la psicosis: el reto de la intervención precoz en los trastornos bipolares

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Historically, mental health services were designed to meet the needs of individuals with persistent psychoses. This strategy arose because schizophrenia was invariably regarded as a chronic neuro-developmental disorder with limited prospects for symptomatic or functional recovery. In contrast, manic depression (or bipolar disorder; BP) was viewed as an intermittent, cyclical disorder associated with full inter-episode recovery that often occurred in otherwise high functioning individuals. Although contemporary clinical studies have suggested that the perceived outcomes for psychosis were unduly pessimistic and those for BP were overly optimistic, mental health service innovations have still tended to be judged by their ability to deliver optimal care and treatment to individuals with schizophrenia.<sup>1</sup> Thus it was understandable that the most radical revision of our approach to mental disorders in recent decades, the 'early intervention' movement, initially targeted individuals at ultra-high risk of, or in the early stages of a first episode of psychosis.<sup>2</sup> Few would argue against this philosophy, as schizophrenia is one of the most devastating chronic diseases of adolescence and young adulthood.<sup>3</sup> However, having now established early intervention services for psychosis, an obvious question is whether we can or should adapt the model for individuals with early onset BP. This paper will review the rationale for early intervention in BP and identify some of the challenges that will need to be

addressed in order to translate early intervention services into a viable approach to BP patient populations.

### Rationale for early intervention in bipolar disorders

In a World Bank study that examined the global burden of diseases in working age adults, BP was ranked 6th.<sup>4</sup> The report highlighted that BP is more debilitating and costly than most major medical disorders and also more burdensome to society than schizophrenia (ranked 8th). Part of the explanation of the latter is that, although BP and schizophrenia have similar peak ages of onset, the overall prevalence of BP spectrum disorders is greater than that of schizophrenia. Furthermore, many of the disabilities associated with BP represent the accrual of adverse effects related to comorbidities and other secondary problems, rather than being an integral part of an underlying neuro-developmental process that often impairs the pre-morbid performance of those at risk of psychosis<sup>5</sup> and/or is apparent at first assessment. As such, BP is considered to be the mental disorder associated with the greatest loss of 'human capital'—an indicator of the significant difference between the individual's initial or future predicted level of achievement (reflecting their pre-morbid adjustment) and their actual functional capacity after the onset of BP.<sup>1,5,6</sup>

Recent research has clarified the current pathways to treatment of individuals with early onset BP and delineated its course and outcome. Studies demonstrate that the median duration of untreated illness (DUI) in BP is about 6–10 years,<sup>7,8</sup> with delayed diagnosis and late introduction

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of appropriate treatment for early onset BP emerging as a universal unmet need, whatever the country, the mental health system or its general accessibility.<sup>9</sup> Early intervention services for psychosis, although sometimes accepting cases of BP or severe unipolar disorder, have neither reduced the DUI for mood disorders, nor been able to improve the uptake of mental health services by individuals with early onset BP<sup>1</sup> (less than 50% seek help). This is unfortunate as, compared to adult onset cases, adolescent onset BP is characterized by lower rates of symptomatic and functional recovery with evidence of greater severity of manic and depressive episodes, more frequent relapses, fewer days of euthymia, and higher prevalence of rapid cycling.<sup>10–16</sup> The latter may be exacerbated by the use of ‘mood destabilizing’ medications in undiagnosed or misdiagnosed cases of BP. Like their adult onset counterparts, adolescent onset BP often exhibits high rates of medical co-morbidities from an early phase, even when compared to adolescents with other mental disorders (36% vs 8%).<sup>15</sup> Very importantly, suicidal ideation, behaviour and attempts are reported to occur more frequently during the earliest stages of BP,<sup>12–14</sup> whilst substance misuse is more often a secondary phenomenon in adolescent BP (BP occurring first in 55–83% cases) than in adult onset BP.<sup>16</sup> Earlier intervention could clearly address some of these as yet unmet needs.

It is well documented that individuals experiencing a first manic episode who are treated with medication in current mental health systems are significantly less likely to experience functional recovery (35–56%) than syndromal recovery (75–95%) over 1–2 years.<sup>10–15</sup> Also, the late introduction of mood stabilizers or psychological therapies is associated with poorer treatment response,<sup>17,18</sup> whilst frequent manic episodes, longer duration of BP and treatment non-adherence are all linked with greater levels of neuro-cognitive impairment.<sup>19,20</sup> Overall, these data suggest that early access to and the provision of multi-dimensional, psycho-bio-social treatments for BP is critical to maximising the probability of treatment response, reducing the impact of the underlying disease process on day to day functioning, and minimising the development of early or late complications and disabilities.<sup>21</sup> Such approaches are synonymous with the philosophy of early intervention.

## Applying early intervention principles to bipolar disorders

Early intervention services often apply clinical staging models to define different levels and targets for intervention.<sup>2</sup> The most commonly identified stages for intervention are: ultra-high risk cases (individuals at risk of ‘transition’ to a first episode of illness); early identification and treatment of first episode cases; and management of the critical period (the first 5 years post-diagnosis).<sup>3</sup>

Recognising ultra-high risk cases in BP is not straightforward. In psychosis research, individuals at risk of transition into first episode cases are often identified by a combination of attenuated or sub-threshold symptoms, accompanied by functional deterioration presenting in the context of other known risk factors—such as a family history of psychosis.<sup>1–3,6</sup> In BP, there are few studies that delineate the equivalent parameters and so far, reported conversion rates are

typically only about 20%.<sup>22–24</sup> There are few symptoms that specifically differentiate the prodromes of first episode mania from those for psychosis or unipolar depression.<sup>25,26</sup> Attempts to define a BP prodrome are further complicated by the fact that the ‘at risk mental state’ potentially comprises multiple symptoms often clustered in different combinations depending on whether the clinical presentation evolves into a manic, hypomanic, mixed or depressive episode.<sup>1</sup> This has led some to focus on ‘enrichment’ strategies to identify those at greater risk of transition to BP, such as the recruitment and prospective follow-up of the offspring of BP parents. Whilst this research approach has identified individuals who will develop supra-threshold mental health problems, it has not necessarily helped clinicians to identify the subgroup of offspring at ultra-high risk of BP as opposed to unipolar or other disorders.<sup>27</sup> Furthermore, even in those who develop BP, the mean age of onset of adult-type hypomania or mania is predominantly between 15 and 21 years (the same peak as the general population), and these episodes have frequently been preceded by depressive episodes or a broad range of developmental psychopathologies of childhood such as non-specific sleep problems, conduct or anxiety disorders.<sup>28,29</sup> An early intervention service in secondary care settings for all such individuals would not be feasible if the target was BP as compared to all affective states. As such, researchers have examined other putative phenotypes for bipolarity, such as severe mood dysregulation, ‘cyclothymia’, cyclothymia, and even pre-pubertal variants of BP (using childhood BP diagnostic criteria). However, all of these again demonstrate low positive predictive value for adult prototype BP.<sup>1,3,6,29</sup> As the reliable and valid identification of ultra-high risk cases remains an aspiration; primary prevention of BP is beyond our present capabilities and is not a viable target for early intervention services for BP. However, this is not an argument against the notion of early intervention in BP, it simply clarifies the most appropriate clinical targets.

For now, early intervention for BP is best directed at early secondary prevention with first episode cases and active management of the critical period in newly diagnosed cases—a strategy that mirrors the approach employed by the majority of early intervention services for psychosis.<sup>2,3</sup> Such interventions represent a worthwhile improvement on current practice which, even in early onset cases, tends towards ‘cross-sectional periods of acute care’, with young adult patients disengaging from the services between BP episodes and missing out on the benefits of continuous care or appropriate management of inter-episode symptoms as well as having limited access to psychosocial or rehabilitative programmes that may improve self-esteem and social functioning. A more coherent approach to BP could begin by looking to improve case finding through raising the awareness of mental health and primary care professionals to the need for more timely and accurate diagnosis of BP, accompanied by offers to train non-specialist clinicians in the use of screening tools for BP. However, this strategy is only justifiable if potential or probable cases of BP are then given early access to a dedicated service that provides structured, comprehensive and age-appropriate interventions including not just medications, but also evidence-based psychosocial approaches, on-going support for the young person (and their family) as they try to adjust to the diagnosis and its

implications, and that adequately address the unique developmental needs of the individual. As was highlighted when advocating services for young adults with psychosis, current mainstream mental health services do not offer adequate continuity of care through the critical period of BP and realistically only a specialist service for individuals with early onset BP is likely to meet their needs, especially as initial presentations are less clearly defined than classic BP syndromes. Considerable skill will be needed to clarify the sub-type of mood disorder, its differentiation from personality or co-morbid disorders and to determine and deliver the most appropriate treatment. There is a relative lack of detailed information on the best pharmacological treatments for early onset BP and the optimal combinations of or timing of introduction of psychosocial therapies and medication. An early intervention service for BP would be an ideal setting to undertake meaningful treatment trials in this specific sub-population of patients (both randomized trials and cohort studies), instead of relying on the strategy of extrapolating from the evidence-base for adult onset cases. Investigations of biomarkers and proximal and distal risk factors for BP onset could also be instigated alongside prospective cohort studies that clarify the progress of early onset mood disorders and predictors of good and poor prognosis.<sup>1,6,30</sup> As such the introduction of such a service would serve the dual purpose of promoting good clinical practice with newly diagnosed cases of BP whilst simultaneously developing the much needed research to enable us to improve the future prospects and outcomes for individuals with adolescent onset BP—a group who have been neglected for far too long.<sup>1</sup>

## Conflict of interest

The author has no conflict of interest to declare.

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