# Prodromal Symptoms of Bipolar Disorder

Subjects: Pathology

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The onset of prodromal symptoms in subjects who are at familial or clinical risk for bipolar disorder could be considered as an important alarm bell for the development of the disease and should be carefully detected. The management of prodromes in bipolar high-risk patients appears to be an important means of prevention; nevertheless, at the moment, there aren't clear and widely shared treatment indications.

Keywords: psychiatry ; bipolar disorder ; high risk ; early intervention ; prodromes ; psychopharmacology

## 1. Introduction

Bipolar disorder (BD) is a severe mental illness that usually begins in the early ages, and its course is associated with high levels of functional impairment and poor quality of life [1].

The high-risk status for the development of bipolar disorder has been defined by familial criteria—the presence of at least one first- or second-degree relative with a lifetime history of bipolar I or II disorder [2]—or clinical criteria—the presence of subsyndromal affective episodes that do not meet full DSM-5 criteria for bipolar I/II disorder for duration and severity [3][4]. Youth who have familial risk for BD and present depression, anxiety, mood instability and subthreshold manic symptoms have a 49% of risk of converting to BD [2][5]. Recent evidence hypothesized BD as a progressive disease, whose trajectory starts from aspecific non-mood symptoms, such as those of childhood anxiety disorders, and continues with depression or subthreshold hypomanic episodes in adolescence and early adulthood, up to the onset of first full mood episode [6][7].

Prodromal symptoms frequently appear prior to the index affective episode. Among them, the strongest predictors of new onset of the disorder are depressive symptoms [8], anxiety [9][10], sleep disturbances [11] and subthreshold hypomanic symptoms [2][12][13][14][15][16]. The identification of these prodromal symptoms is important to play out early intervention strategies that could prevent or delay progression of BD, decreasing the total time of illness and mitigating neuroplasticity adverse effects due to repeated mood episodes [17][18].

Furthermore, planification of an early intervention is of particular importance to reduce the time interval in the absence of adequate treatment. The time interval between the onset of the prodromal phase of the disorder and the initiation of proper treatment is defined as duration of untreated illness (DUI), and it is associated with a worse course of the disease, poor level of remission and social functioning, and greater relapse rates and suicide attempts (Ienciu et al., 2010; Buoli et al., 2020) [19][20].

Literature on this topic is still lacking and often provides conflicting results. There are wide debates on the utility of starting a treatment prior to the onset of a full-blown disorder in subjects who may not develop the disease in the future. Possible options for the treatment of subthreshold bipolar symptoms include pharmacological treatment, psychosocial intervention, and nutraceutical intervention.

No guidelines are available for administering preventive psychopharmacological medication for the high-risk population [10][21][22][23]. Each pharmacological treatment is burdened by a series of adverse events and risks, which, in some circumstances, outweighs the benefits. Pharmacological approaches in at-risk populations have often shown a lack of real efficacy [24]. Nevertheless, some compounds used in the treatment of bipolar disorder are also widely used for the management of the above-mentioned symptoms in clinical practice [25].

Psychotherapy seems to be the most suitable intervention in subjects who have not already manifested a real mood episode, due to minimal adverse effects. Psychological therapies have effect on several brain regions involved in the pathogenesis of bipolar disorder, such as the amygdala, insula and anterior cingulate [26]. Psychoeducation and cognitive-behavioral therapy, which focus on providing psychoeducation on symptoms, symptom management and cognitive regulation, are the most studied psychosocial interventions in this population. Some of these psychotherapy models have

been modified and adapted to the needs of specific at-risk youth and adolescents. One example is Interpersonal and Social Rhythm Therapy (IPSRT), which directly targets specific sleep disturbances such as dysregulation of circadian patterns and total sleep time [27][28]. Another method is mindfulness-based cognitive therapy for children (MBCT-C), a specifical intervention for the management of anxiety symptoms and emotional regulation in children who are at risk for bipolar disorder [29]. The most recent systematic review exploring psychosocial interventions in 'at risk' populations was updated until 2019 and highlighted a variety of positive outcomes in the decrease of symptoms [30].

Nutritional supplements are a suitable option for primary prevention because of the relative lack of adverse events. Even if in several cases the efficacy of these compounds appeared inconsistent, some nutraceutical agents have shown promising results (i.e., fatty acids and N-acetyl cysteine for depression, amino acid drinks and folic acid for mania).

Two recent reviews gather the available nutraceutical interventions in the treatment of BD for analysis. They both evaluate the current evidence on the efficacy of improving symptoms by adding nutraceutical agents to psychopharmacological drugs, including long chain polyunsaturated fatty acids (PUFAs), antioxidant agents such as N-acetylcysteine (NAC), amino-acid adjunction or depletion, melatonergic compounds, vitamins such as folic acid, probiotics, other compounds—such as coenzyme Q10—involved in mitochondrial biogenesis, and combination of different types of nutraceuticals (Fusar-Poli et al., 2019) [31][32].

The aim of the present review is to collect and summarize the available treatment options (pharmacological, psychosocial and nutraceutical) for the management of prodromal symptoms in subjects who are at familial or clinical risk for BD.

## 2. Development and Findings

The individuation and the management of prodromal symptoms has attracted interest for the prevention and planification of tailored care in psychiatry. Although clear indications and guidelines for the management of prodromal symptoms in at-risk subjects for BD are still lacking, the available literature has provided a series of positive results.

The existing literature on pharmacotherapy for individuals at high risk for BD provides little overall evidence of benefits and is not supported by sufficient evidence. Pharmacology treatment is burdened by a series of weighty side effects, so its beginning is intended for more severe symptoms and should be evaluated after an accurate assessment of the risk/benefit ratio. The risk linked to antidepressant medications in youths at high risk for developing BD suggests that alternative interventions are needed for the treatment of prodromal depression and anxiety. BZDs should also be avoided due to the risk of misuse and dependence. Low doses of trazodone and mirtazapine (up to 100 mg/day for trazodone, 3.75–15 mg/day for mirtazapine and up to 25 mg/day for agomelatine) have a good safety profile, with low rates of switching [33], and could be considered as important alternatives to hypnotics. Lurasidone and aripiprazole have evidenced a favorable safety profile; the first one has provided good results on both depressive and hypomanic subthreshold symptoms, while the second one appeared efficacious on hypomanic symptoms.

Psychotherapy is the most studied intervention for at-risk populations. Adapted models of CBT (cognitive behavior therapy for insomnia for bipolar disorder and mindfulness-based cognitive therapy for children), IPRST and psychoeducation appeared efficacious and relatively safe and seem to be the best option for high-risk states. The involvement of the whole family, provided by FFT, appeared to be of great importance; improvement in communication and emotion regulation appeared to be useful for the management of depressive, anxious and hypomanic symptoms. Conflicting results are found regarding the use of nutraceuticals. Adjuvant treatment with omega-3 and NAC have shown mild but proven positive results on depressive symptoms and anxiety; however, too few studies have been conducted on the other nutraceutical agents. The use of such supplementation does not reach evidence for recommendation in clinical practice due to scarcity of controlled studies, heterogeneity of methods and results, and important limitations (great variability in inclusion criteria, small sample size and follow-up time).

This study presents some limitations. Above all, it was not organized as a systematic review, so it was not conducted according to PRISMA guidelines. No structured tables were used due to the heterogeneity of the studies analyzed, so the results section might not appear clear. Only one database was searched, and the protocol was not pre-published.

At the moment, evidence in the literature is still insufficient for drawing up shared guidelines about the treatment of psychiatric symptoms that at-risk patients for BD have already manifested. Our review could stimulate new perspectives on research in the field, on the basis of available data. Many of the suggested treatments lack the solid evidence necessary for formal recommendations, so further and more structured studies are needed.

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