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Toward prevention of bipolar disorder in at-risk children: Potential strategies ahead of the data

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Abstract

Background: Despite the well-documented negative impact of untreated bipolar illness, approaches to early intervention in childhood-onset bipolar and related disorders are not well delineated.

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Declaration of Competing Interest

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Methods: We reviewed the extant treatment literature on children at high risk for bipolar disorder, with definitions based on family history, childhood adversity, and prodromal symptoms.

Results: A panoply of approaches have been described, but most interventions are based on an inadequate database to support their routine implementation. We classify early stage interventions as a function of their safety and tolerability with the hope that these might generate more rigorous study and a stronger database.

Limitations: Critics may rightly argue that identifying viable treatment methods is premature given our lack of ability to reliably predict illness trajectory in very young children. However, many of the psychosocial and pharmacological interventions we present could have nonspecific positive effects across a variety of symptoms, syndromes, and diagnoses, further enhancing the rationale for more rigorous study.

Conclusions: Early stage interventions have the potential to improve functioning in prodromal illness and exert long-term positive effects on the course of illness. Many of the safest interventions deserve consideration for implementation and dissemination studies.

Keywords

Prodromes; Genetics; Epigenetics; Psychopharmacology; Psychotherapy; Early intervention; Depression; Anxiety

1. Introduction: purpose of this commentary

Bipolar spectrum disorder (BPSD) in children is common, impairing, and with lifelong consequences for premature mortality from suicide and increased cardiovascular illness. Clinicians and parents often attempt to ward off, delay, or mitigate the adverse effects of childhood onset bipolar disorder and its related comorbidities. In this article, childhood onset bipolar disorder (BD) refers to the spectrum of BP-1, BP-II, and unspecified BP (or formerly, BP-not otherwise specified [NOS]), unless other stated. It is not clear what clinicians should do when there are few data and few accepted evidence-based recommendations for these conditions. In this article we review the sparse data on early intervention in youth who are at high risk for bipolar disorder, and describe innovative psychosocial and pharmacological treatments that may be worthy of consideration. We suggest explorations of the effectiveness of certain early intervention approaches as a way of moving the field forward. While prevention-oriented interventions have been described, the data on them are insufficient, and a new round of more concerted study is needed.

Many clinicians and families are interested in possible preventive approaches in children at high risk by virtue of a positive family history of BP and other risk factors (Findling et al., 2013; Findling et al., 2005; Hafeman et al., 2016; Hafeman et al., 2017; Post et al., 2013). Parents and clinicians deserve to know what is at least reasonable to consider for children at high risk. We have attempted to consider and integrate information on each potential intervention covered in this review as to: its safety and tolerability, its direct or indirect evidence of effectiveness in other populations and age groups, and the strength of its clinical or theoretical rationale.

Given the acknowledged paucity of data, these preliminary opinions are subjective and meant to be revised as more experience with a drug or psychosocial treatment is acquired. We acknowledge that most of the treatment suggestions we outline here lack the necessary supporting data that would ordinarily make them scientifically acceptable for formal treatment recommendations or guidelines (Hu et al., 2017; Post, 2016a; Post, 2016b: Post et al., 2017b). It is hoped that the obvious and glaring deficit of knowledge on this problem of huge public health significance will generate innovative research to fill these gaps. It is also hoped the ideas shared herein will inspire case series, open trials, and, ideally, gold-standard, randomized controlled trials.

2. Methods: arranging suggestions according to the stage of illness evolution

We and others have postulated that bipolar disorder is a progressive illness with definable stages of evolution (Berk et al., 2017b; Kapczinski et al., 2009; Post, 2015; Post, 2017b). In this manuscript, we discuss treatment intervention possibilities as a function of stage of illness, a variable that is related to age (and by definition, risk status). There are many different staging models for bipolar disorder, but we chose to use one that is more detailed than most, as this might facilitate consideration of the most focused treatment targets. In this schema (Post, 2015; Post 2016a; 2016c), stages are categorized as follows:

Stage I is “At Risk”, and includes genetic and perinatal risk factors, such as low birth weight, quality of prenatal care or maternal infection.

Stage II is “Well Interval” and it occurs prior to the onset of prodromal or syndromal symptoms. It could include environmental risk factors that might occur in childhood such as abuse, infections, or loss of a parent.

Stage III is “Prodrome”, consisting of symptoms that are homotypic or similar to those occurring in syndromal bipolar disorder, such as mood instability. Others are heterotypic prodromes or syndromes not necessarily related to bipolar disorder, such as anxiety disorder, ADHD, oppositional defiant or conduct disorder, or substance abuse, each of which may precede a bipolar diagnosis.

Stage IV is “Onset” and can reflect the first full episode of BPI or BP II disorder.

Stages I to IV will be the major targets of this discussion, with the view that these early stages are often over looked, while the later stages (V: “Recurrence”; VI: “Progression”; VII: “Treatment Resistance”; and VIII: “Late or End stage”) often have at least a modicum of data on treatment and are typically the stages dealt with in treatment guidelines. In both children and adults, treatment of bipolar disorder too often begins after these later stages have occurred, and too often with disappointing results.

As in most staging models, it is hoped that earlier and more effective treatment interventions may prevent, delay, or reduce the impact of the later stages. Early intervention is also essential to minimizing illness progression and the sensitization to episodes, stressors, and

substances of abuse, and their underlying epigenetic changes (Post, 2016a; Guintivano and Kaminsky, 2016)

For example, there is considerable evidence in adults that outcomes are more favorable if lithium is started after an initial hospitalization for mania (Kessing et al., 2014a; 2014b), and lithium as well as many other interventions in adults appear to be more successful when initiated after the first few episodes (Post et al., 2012). The 10 year longitudinal follow up study of Geller et al (2010) found that those who had been treated with lithium did the best and had the most time in remission. Similarly, Hafeman et al (2019) reported on a total of 340 children with bipolar disorder 7–17 years old over a mean follow-up of 10 years of naturalistic treatment. After covariate adjustment (including age, age at bipolar onset. family history of mania, race SES, sex, and site), the lithium group (compared to those treated with other mood stabilizers) had half as many suicide attempts, fewer depressive symptoms, less psychosocial impairment, and less aggression. These authors concluded: “Given the paucity of evidence regarding lithium in children and adolescents, these findings have important clinical implications for the pharmacological management of youths with BD.” More generally, the earlier stages and younger ages of children with prodromal symptoms suggest interventions with the highest record of safety and fewest side effects.

3. Scope of the problem

The treatment of youth at high risk for schizophrenia or with prodromal psychosis symptoms has been studied relatively extensively for more than two decades (Lieberman et al., 2019). Disappointingly, there are few such studies of BP and its related comorbidities. The functional impairment, comorbidity, and symptomatic burden of bipolar spectrum disorders in childhood are comparable to those of full-fledged bipolar I and II disorder in adulthood. Even recurrent fleeting manic symptoms in youth can be associated with substantial impairment (Birmaher et al., 2009; Findling et al., 2013). There is a misconception that these cases are subclinical and do not require treatment, potentially contributing to the dearth of treatment studies for prodromal and spectrum manifestations of BP. There are also fears of treating young children with powerful medications and/or exacerbating illness with antidepressant or stimulants.

Epidemiological studies find that manic episodes occur in 2.5% of U.S. adolescents; other studies indicate that the prevalence may be as high as 4–5% if children with BP-NOS are included in assessments (Lamers et al., 2013; Van Meter et al., 2011). BP-NOS is the most common presentation in young at-risk children, and can be quite impairing (Birmaher et al., 2009). In their latest review, Van Meter et al (2019) found 3.9% of youth had a bipolar spectrum disorder with 0.6% having a BP I diagnosis and 6-fold more having cyclothymia or BP-NOS. Youth with BP-NOS convert to full-blown BP I or BP II illness in 30–50% of cases at 5–8 year follow-up, with higher rates among those with first-degree relatives with mania (Axelson et al., 2015; Birmaher et al., 2009; Birmaher et al., 2018; Hafeman et al., 2016).

Studies of adults with bipolar disorder in the US reveal that about 25% experienced their first episode of mania or depression before age 13 (Etain et al., 2012; Perlis et al., 2004; Post

et al., 2017a), and 63–69% before age 19. Substantially fewer onsets of child/adolescent bipolar disorders (25–42% of adults with BD) are found in European studies or on other continents (Bellivier et al., 2014; Etain et al., 2012; Post et al., 2017). Early onsets are associated with longer delays to first treatment, and both early onset and longer treatment delay are risk factors for a poor outcome of bipolar disorder in adults (Post et al., 2017; Post et al., 2010). Merikangas et al (2010) indicated that only around 20% of adolescents age 13–18 diagnosed with a bipolar spectrum disorder received any kind of treatment at all. Thus, large numbers of children with substantial burdens of illness are not being treated, in part due to a paucity of systematic clinical treatment studies in the literature.

Several striking findings are revealed in the Pittsburgh Bipolar Offspring study, where 49% of offspring with (1) a parent with an early diagnosis of bipolar disorder and (2) anxiety, depression, mood instability, and subthreshold mania or hypomania received a bipolar spectrum diagnosis upon 8 years of follow up, compared to a 2% rate in offspring of bipolar parents without childhood onset and without these early symptomatic risk factors (Hafeman et al., 2016). Yet, a diagnosis of any major childhood psychiatric disorder occurred in 74% of the children of a parent with bipolar disorder, with more than 20% in each of the following categories: major depression, anxiety, ADHD, ODD, and substance abuse (Axelson et al 2015).

4. Assessment of risk status

Some might argue that prodromal and preventive intervention studies should wait for definitive and illness-specific neurobiological markers of those at high risk. To date, neurobiological markers (such as CACNA1C, ANK3, or alleles of brain-derived neurotropic factor) have not informed prediction of an ultimate diagnosis of BD or the selection of treatments. However, using three currently available clinical indices can robustly quantify risk. First, I.) *clinical and family history* variables allow one to identify high and very high risk status (Findling et al., 2005; Post et al., 2013). A positive family history of bipolar disorder is a potent risk factor, but a history of multiple psychiatric diagnoses in parents and grandparents is associated with an even earlier age of onset of bipolar disorder (Post et al., 2015b,Post et al. 2015c; Post et al., 2018; Post et al., 2016b; Post et al 2016c).

Second, if family history variables are combined with the occurrence of II.) *adversity in childhood*, such as verbal, physical, or sexual abuse, risk is further heightened. The age of onset of bipolar disorder in the US averages below age 13 (Post et al., 2016c); the average age of onset is 26 years if there is neither a positive family history of bipolar disorder in parents or grandparents nor a history of childhood adversity. A history of only verbal abuse in childhood (in the absence of physical or sexual abuse) is also associated with an earlier onset and a more difficult course of bipolar disorder in adulthood (Post et al., 2015a). Aas et al (2016) reports more than a dozen studies linking childhood adversity to a more difficult course of illness in early onset bipolar disorder. They also cite 6 studies reporting adversity as a risk factor for BP onset. Maniglio (2013) discussed 20 studies linking a higher incidence of adversity in families with a bipolar offspring versus controls.

Third, if one then adds III.) the presence of *prodromal symptoms*, risk status is further increased. The type of prodrome can also be delineated along with the likelihood that it will be associated with substantial dysfunction, and thus in need of intervention independent of the eventual transition to full syndromal bipolar disorder. These variables would have some similarities to what Correll et al (2014; 2007) would consider “familial high risk” and “clinical high risk”.

To these three risk variables one could later add neurobiologic markers as they become available. These could include genetic markers (such as CACNA1C and ANK3), as well as other abnormalities such as inflammation, brain imaging abnormalities, and obesity. Since risk can already be preliminarily delineated from low to very high on the basis of these available clinical and history variables, the degree of risk can readily be integrated into decisions about the appropriateness of attempts at early intervention and prevention. An overriding principle for the interventions suggested in this article is that the younger the child and the lower the risk status, the more that safe and well-tolerated treatments should be the first considered. Moreover, as age, risk status, stage of illness, and especially the degree of dysfunction increase, more diverse approaches with the potential for side effects could be increasingly considered.

Hafeman et al (2016, 2017) in their risk calculator for conversion of BP-NOS to BP I or II in the Pittsburgh Bipolar Offspring study, cited the following risk factors in offspring of parents with bipolar disorder: elevated depression, anxiety, or mood instability scores in childhood and throughout follow-up; being female and white; and an earlier parental age at onset of their own bipolar disorder. Protective factors included high socioeconomic status and growing up with both biological parents. However, even an accurate assessment of these factors and the associated risk of onset of BP would not inform what type of treatment would be most promising.

5. Further rationales for early intervention

Even if the field waits for definitive risk markers, once they did arrive we would still need the kinds of early intervention studies discussed here of the available and/or new treatment options. Identification of a biomarker with prognostic utility may not translate into better interventions. Parenthetically, recent discussions with several world renowned geneticists (RMP, personal communication, Dec, 2018), revealed their pessimism in finding actionable genetic markers for bipolar illness at any time in the near future, aligning with the reality that, aside from psychiatric manifestations of known rare genetic illnesses, there are no genetic tests for the overwhelming majority of people with any of the major psychiatric illnesses.

Another potential argument against the implementation of early intervention studies is that the early symptoms are hard to characterize, are pleomorphic and lack specificity. The pathways to specific illnesses are opaque and show a pattern of multifinality of trajectory to many ultimate diagnoses. However, we would argue that this heterogeneity of symptoms and outcomes can be converted into an advantage for proceeding with studies of early interventions. This is because many of the earliest and safest potential

interventions themselves do not appear to have illness specific effects, but preliminary positive effectiveness data across a variety of syndromes. So assessing whether, for example, omega-3-fatty acids had positive effects in depression or ADHD, whether or not they helped prevent or delay the onset of bipolar illness, would still be valuable. In this way we would be using some of the same principles endorsed by the Research Domain Criteria (RDoC), but in reverse. RDoC posits that many syndromes and illness have common pathophysiologies and pathways (Insel, 2014). However, instead of the current RDoC strategy of looking for a common molecular target for new drug development, we instead encourage the more immediate study of existing interventions that target common mechanisms.

Inflammation and oxidative stress would be good examples of processes now linked to multiple psychiatric and medical illnesses (Goldstein et al., 2016). Several of the drugs we discuss act nonspecifically on these variables, so assessment of which syndromes respond or not to these agents would be clinically and theoretically valuable even in the absence of evidence that they help prevent the onset of bipolar disorder.

The same can be said for many of the suggested psychosocial therapies and public health interventions: they are safe and likely to be effective across a variety childhood prodromes and illnesses, possibly suggesting common mechanisms. For example, family focused therapy (FFT), which was originally modeled after behavioral family therapy for schizophrenia (Falloon et al., 1985), appears effective for depression, BP-NOS, prodromal psychosis, and bipolar I and II illness (Miklowitz and Chung 2016; Miklowitz et al., 2013; Tompson et al., 2017). Given in 12–18 sessions for 4–6 months, FFT engages children, adolescents or young adults in sessions with parents and other caregivers, in which they (a) learn about mood management strategies through psychoeducation, and (b) learn to communicate and solve problems more effectively though behavioral rehearsal.

FFT, when given during the high-risk interval prior to full bipolar onset, is associated with more time in remission and longer intervals prior to mood recurrences than are briefer comparison treatments (Miklowitz et al., 2013; 2020). FFT may work in multiple psychiatric disorders where family members (in their well-meaning attempts to make sense of the untenable and the stigmatizing situation of having an offspring with psychiatric problems) often become highly critical, overprotective, or overly controlling, which in turn may slow the pace of recovery in the offspring. Indeed, high “expressed emotion” in caregivers (high levels of criticism, hostility, or emotional over involvement (Peris et al., 2015)) has been linked to increased rates of relapse in various mood and psychotic disorders, and may be a moderator of response to family intervention (Miklowitz et al., 2009).

A final rationale for considering treatment interventions ahead of adequate systematic supporting evidence is that treatments could be studied first in pilot studies, case series, and naturalistic outcome studies, and followed by more systematic open randomized studies, and then gold-standard randomized placebo controlled clinical trials (RCTs). If approaches do not look promising in initial open studies, expensive RCTs might be avoided. In high risk children who are already prodromal, treatment choices would also vary depending on the degree of symptom severity and impairment, which might warrant intervention with more risky agents, such as atypical antipsychotic or mood stabilizers. In contrast, mild anxiety

might merit cognitive-behavioral therapy, lifestyle optimization, and supplements generally regarded as safe, prior to introducing major psychopharmacology (McNamara et al., 2010).

6. Results: interventions as a function of stage of illness evolution

We outline approaches that might be considered according to the earliest stages of illness evolution: Stage I, Vulnerability; II, Well Interval; III, Prodrome; and IV, Onset. Suggestions for these interventions can be roughly sequenced on the basis of their safety, direct or indirect evidence for likely effectiveness, and the strength of the clinical or theoretical rationale (Table 1). Each intervention can also be considered and integrated with the strength of the at-risk state ranging from lowest to highest risk, and the presence of an already symptomatic prodromal or syndromal state. We have used the Grade system 1 from UpToDate to preliminarily grade our suggestions in Table 1. This system characterizes recommendations as either: 1 strong and 2 weak; and then grades the quality of the evidence as: A, high; B, moderate; C or weak. It is readily noted that most suggestions discussed here are graded 2C because inferences on likely effectiveness are often based on data in other conditions and/or in adults instead of children, as well as from low quality observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. We have starred (*) the suggestions that might be good universal recommendations not uniquely beneficial for those at risk for bipolar disorder. However, their utility in mitigating the risk for onset of child and adult psychiatric and medical illnesses should not be discounted, and greater efforts in making these health maneuvers more universal would be recommended.

6.1. Stage I. vulnerability

Folate should be considered during pregnancy, especially for first trimester use as it is known to help avoid spina bifida, language delay, and deficient development of prefrontal cortex. However, there is some controversy about the effect of high dose folate on autism (Wiens et al., 2017). One would consider l-methylfolate instead of folate for those with the MTHFR deficiency (when folate itself is insufficient)

Vitamin D 3 should be considered given that low or deficient levels have been found in a high proportion of children with psychiatric illness, even if the data on prevention effects using this vitamin are not yet compelling (Chauhan et al., 2019; Gracious et al., 2012; Zeng Q et al., 2016).

Phosphotidylcholine is known to address and prevent the P50 sensory gating abnormality that is present in patients with schizophrenia and bipolar disorder. Ross et al (2016) gave 3600 mg in the morning and 2700 mg in the evening to mothers in the second and third trimester, followed by supplements for the infant (100 mg/day for 12 weeks). However, an accompanying editorial by Rapoport (2016) suggested that clinical extrapolation of these findings might be premature, and instead encouraged a good diet and prevention of infection. The choline supplementation would be roughly equivalent to 3 eggs/day.

A good diet during pregnancy may help prevent maternal obesity and high omega 6 fatty acids, which convey inflammation and may increase the life long risk of obesity and behavioral disorders in the offspring (Gaillard, 2016; Poston, 2011).

Careful and adequate treatment of mother's depression prepartum will help avoid the associated low birth weight and premature delivery with their attendant risk for later psychiatric illness in the child, although the risk benefit ratio needs to be discussed with each family when one is considering pharmacological treatments.

Adequate interventions targeting sleep/circadian rhythm stabilization across pregnancy and the postpartum period, may help prevent postpartum mood episodes (Gallaher et al., 2018; Krawczak et al., 2016; Owais et al., 2018).

Parental avoidance of alcohol and drugs (even prior to pregnancy) is also to be encouraged in light of new data on multigenerational transmission of some parental behavioral and biochemical abnormalities based on epigenetics (Post, 2016a; Guintivano and Kaminsky, 2016)

6.2. Stage II well interval

Treatment of mothers' post partum and later depressions to full remission is associated with fewer internalizing and externalizing psychiatric illnesses in the offspring (Weissman et al., 2014; Wickramaratne et al., 2011). Added psychosocial support should be considered for the postpartum mother regardless of depression status. One could encourage newborn support groups and help with maternal time outs; education in child rearing practices; and the consideration of using a visiting nurse which is known to reduce behavioral problems in families at high risk (Casillas et al., 2016; Olds et al., 1998). For a school-aged anxious child, mindfulness-based cognitive therapy (Cotton et al., 2016; Strawn et al., 2016) and related interventions may be helpful.

For the newborn, infant, and young child, one could explicitly encourage a good diet, and consistent exercise and sleep hygiene. A focus on teaching self control and the ability to delay gratification is associated with life long socioeconomic benefits (Moffitt et al., 2013).

For older and school-age children, exercise in general and/or participation in team sports should be encouraged regardless of athletic prowess, and music lessons and practice are known to increase cortical development (Hudziak et al., 2014). A good diet and specific prescriptions for exercise may be helpful in enhancing fitness, if not in warding off the current epidemic of obesity, especially since obesity is linked to CNS abnormalities, cognitive dysfunction, and poorer outcomes in those who do develop syndromal bipolar illness.

For adolescents who have not developed a mood disorder, but whose parents had a bipolar I or II disorder, an average of 4 sessions of interpersonal and social rhythm therapy had small but positive effects on sleep continuity, which may protect the teen against later onsets of mania or hypomania (Goldstein et al., 2018).

For these older children who are additionally at higher risk because of the experience of childhood adversity there could be greater emphasis on and more intensive application of the above recommendations, and in addition use of group psychoeducation and family focused therapy (FFT) or its equivalent (Miklowitz et al., 2013). Richmond-Rakerd et al (2019) endorse transdiagnostic approaches that teach self regulation.

One might consider use of acetyl-L-carnitine which is low in the blood of adult depressed patients, especially in those with early onset and those with a history of childhood adversity (Nasca et al., 2018). Acetyl-L-carnitine has antidepressant effects in both humans and animals subjected to stress-induced depression-like behavior. Acetyl-Lcarnitine may have a prophylactic effect on depression by an epigenetic mechanism in increasing the production of the metabotropic glutamate receptor mGluR-2, which inhibits excess glutamate release. In animal models of depression mGluR-2 is low and behavior is rapidly normalized with acetyl-L-carnitine in a matter of days as opposed to antidepressants which take weeks. In light of the theoretical possibility that this mechanism of acetyl-L-carnitine could convey prophylactic effects, the drug might be considered for children who have experienced childhood adversity who already have syndromal depression (Post, 2018). Such a study should have a very high priority given the multiplicity of difficult medical and psychiatric illness associated with toxic stress in childhood (Shonkoff and Garner, 2012).

For those children who are at high risk and are showing anger dyscontrol: facial emotion recognition training could be considered, as deficits in facial emotion recognition are present in at-risk children as well as those with childhood and adult onset bipolar disorder (Brotman et al., 2008). Preliminary data suggest that this can be successful in enhancing emotion recognition and greater ability to discriminate positive from negative and angry faces. Whether such training would ultimately improve behavioral reactivity and social interactions remains to be demonstrated.

The potential for supplementation with omega-3-FA also deserves consideration (McNamara et al., 2016).

6.3. Stage III prodrome

Axelson et al (2015) reported that other diagnoses of major depression, ADHD, ODD, and anxiety disorder preceded the diagnosis of a bipolar spectrum disorder 35 to 45% of the time, and more rarely occurred at the same time as onset or after onset. Any diagnosis preceded the onset of bipolar disorder 93% of the time, but followed the onset only in 6.9% of instances. McNamara et al (2010) discuss a variety of potential early intervention strategies.

6.3.1. Heterotypic prodrome, such as anxiety, ADHD, and ODD

6.3.1.1. Anxiety disorders.: There are a host of positive studies of cognitive-behavioral therapy in anxiety disorders, and SSRI are widely used in children. Whether use of SSRIs in children at high risk for bipolar disorder by virtue of a parental history would incur any additional side effects remains to be specifically studied.

Data for N-acetylcysteine are positive for anxiety in adults with bipolar disorder and as an adjunct to SSRIs in OCD and in avoiding many substances of abuse. It also helps irritability in autism (Ashton et al., 2019), so safety in children has been demonstrated. Effects on an isolated anxiety prodrome have not been studied.

Frazier et al (2012) reported good effects of EM Powerplus in a small open series of patients with aggression and dyscontrol some of whom did not respond to conventional antimanic agents.

In contrast to lithium where anxiety disorder comorbidity in adults is a predictor of non-response, the mood stabilizing anticonvulsants have some positive effects in adults with anxiety disorders (Post and Leverich, 2008). Although lithium response in adults is associated with a positive family history of mood disorders, a personal or family history of an anxiety disorder is a predictor of response to lamotrigine in patients with bipolar I or II illness (Duffy et al., 2007; Passmore et al., 2003). Very low, slow dose increases of lamotrigine are recommended to avoid a severe rash. Whether any of these indirect inferences from prediction of response in adults are pertinent to children remains to be investigated.

6.3.1.2. ADHD.: Stimulants remain the treatment of choice for children with uncomplicated ADHD and these can be combined with an alpha-2 agonist. In those with ADHD in concert with prominent bipolar symptoms, most authorities would recommend mood stabilization prior to the use of stimulants. The potential role of stimulants in triggering a manic episode is controversial, as discussed in detail by Soutullo et al (2002) and Goldsmith et al (2011). The latter article concludes “There is no clear evidence that stimulants or SSRIs accelerate the natural course of BD development in overall samples, but in individual cases prescribers should proceed cautiously when using these agents in youth already at risk for developing BD, such as those with ADHD and mood dysregulation, a history of prior AIM (antidepressant-induced mania), a history of psychosis, or a family history of BD.”

Modafinil could be helpful in those not tolerating stimulants. Atomoxetine has considerable positive data in ADHD often with other comorbidities (Hutchison et al., 2016), but its potent noradrenergic effects in those at risk for bipolar disorder should be carefully considered given the higher risk of switches into mania with antidepressants with noradrenergic potency.

6.3.2. Homotypic prodromes, such as depression, cyclothymia, and BP-NOS

6.3.2.1. Depression.: For Omega-3-FA there are some positive data in adults and in one study of “younger” (<45), but not older (>45) adult bipolar patients with depression (Keck et al., 2006). The data on prevention of progression of the prodrome in schizophrenia are intriguing including on long term follow up of 6.8 years (Amminger et al., 2015). A new study by McGorry et al (2017) did not replicate these finding, but there were many potential explanations including the high use of antidepressants, high rates of non-adherence, and the concomitant use of cognitive-behavioral interventions in both arms, Interestingly, Pawelczyka et al (2015) reported success of omega-3-FA.in decreasing the rate

of relapse after a first episode of schizophrenia. Preliminary and open studies in the bipolar spectrum are promising (Bozzatello et al., 2016; Fristad et al., 2015; Wozniak et al., 2007). Vesco et al (2015) reported positive effects over several years in a children with psychotic mania and comorbid anxiety. Other positive data on omega-3-FA, often in conjunction with psychotherapy, have recently been reported (Arnold et al., 2017; Fristad et al., 2019; Fristad et al., 2015; Vesco et al., 2018; Young et al., 2017). Yet in a recent interview (Nasir and Block, 2019 and a meta-analysis (Zhang et al., 2019), the endorsement of omega-3-FA was less than enthusiastic.

N-acetylcysteine has positive data in bipolar depression in adults and in multiple common comorbidities of bipolar disorder including substance abuse (Berk et al., 2013). Safety in youngsters is demonstrated in 3 positive placebo-controlled studies on irritability in children with autism.

Lurasidone has been studied in adults and in youth 10–17 with bipolar depression where it was found highly effective and very well tolerated (DelBello et al., 2017).

For other atypical antipsychotics, there are also positive data for children with bipolar spectrum disorders for risperidone (Geller et al., 2012), quetiapine (DelBello et al., 2007) (but not adolescents with bipolar depression (DelBello et al., 2009)); and aripiprazole (Findling et al., 2017), but each, in contrast to lurasidone (DelBello et al., 2017) and ziprasidone (Dominick et al., 2015; Findling et al., 2013) (which failed in adult bipolar depression studies) was associated with considerable weight gain.

SSRIs are widely used in youngsters with depression, but Strawn et al (2014) reported that in 108 youth who had a parent with bipolar disorder followed for 26 months that those treated with antidepressants became more irritable, aggressive, impulsive, and hyperactive leading to medication discontinuation. In a small study, Findling et al (2008) did not find paroxetine with or without valproate helpful. He also reported that valproate was not more effective than placebo in those with cyclothymia or BP-NOS (Findling et al., 2008). Geller et al (2001) found high rates of switching on nortriptyline in those with childhood onset depression. Therefore, the use of other, safer treatment modalities are preferred over SSRIs in this population.

In light of lithium's effects in unipolar depression and the prevention of suicide (Abou-Saleh et al., 2017; Post, 2017; Tiihonen et al., 2016), it deserves to be studied in high risk children with depression and other disorders (Ando et al., 2017).

Family-focused therapy or psychoeducation may be useful in any prodromal child. In two trials ($N = 40$ and $N = 127$), both involving youth with major depression or BP-NOS, Miklowitz et al (2013; Miklowitz et al., 2020) found 12 sessions of FFT to be highly effective in reducing depressive symptoms and delaying new mood episodes over 1–4 years. Similarly, Nadkarni and Fristad (2010) found that among 37 children (ages 8–12) with depressive spectrum disorders plus transient manic symptoms, those receiving Multifamily Psychoeducational Psychotherapy had fewer conversions to bipolar spectrum disorder (16%) than those in a wait list control group (60%) over 12 months of the study.

7. Stages II to IV with inflammation

If any of the inflammatory cytokines (Il-I, Il-6, TNF alpha, or CRP) are elevated, one could consider:

1. Minocycline. Rosenblat and McIntyre (2018) have reviewed promising data in depression. Minocycline inhibits the activation of microglia so it should decrease TNF alpha. Bipolar, depressed patients with higher Il-6 at baseline improved more with minocycline acetylsalicylic acid plus placebo aspirin than those with placebo minocycline with aspirin (Savitz et al., 2018).
2. celecoxib. In adults with BP depression, Castillo et al (2019) reported that compared to placebo, celecoxib was more effective when added to ineffective antidepressant treatment. Results were best in those with baseline indicators of inflammation.
3. When CRP is elevated, one might consider lurasidone, which is associated with greater improvement in adults with bipolar depression with elevated CRP at baseline (Raison et al., 2018). Similar findings have been reported in children 10–17 treated with lurasidone for bipolar depression. (Raison et al., 2020)

7.1. More severe BP-NOS with a predominance of mania

In BP-NOS, a consensus is forming toward the need for pharmacological treatment, with the benefits out weighing the risks. Compared to youth with BP I or II, youth with BP-NOS have nearly as much psychosocial impairment, take longer to stabilize from episodes; have as much comorbidity, suicidality, and substance abuse; and are just as likely to have first-degree relatives with BP I or II (Birmaher et al., 2009; Wozniak et al., 2017). As indicated earlier, about 50% of children with BP NOS and a family history of mania convert to BP I or II over 5–8 years (Axelson et al., 2015; Hafeman et al., 2016).

One could consider the adjunctive use of vitamin D3 or folate along with lithium for those with severe BP-NOS, especially if family history is positive for lithium response (Duffy et al., 2007). However, Geller et al (1998) failed to find that lithium was more effective than placebo in a small study ($N = 25$) of youth with BP I.

Oxcarbazepine (OXC) was positive for the youngest, but not oldest children with full blown bipolar disorder (Wagner et al., 2006). Since the youngest children with a bipolar spectrum disorder typically present with BP-NOS, some clinicians might consider oxcarbazepine as a safer alternative to carbamazepine for those with severe BPNOS, although further direct data are required to support this suggestion.

Valproate (VPA) could be considered but not for females of childbearing age. Further, Findling et al (2007) found VPA no more effective than placebo in those with BP-NOS and a positive history of bipolar disorder in a parent.

One should use well-tolerated atypical antipsychotics (AAs) in preference to those better tested and documented in mania (i.e., olanzapine, which has a considerable adverse side effects profile, including weight gain and other aspects of the metabolic syndrome). It may

be useful to consider an A.As. with evidence of effectiveness in depression and depression prevention such as quetiapine or lurasidone, instead of aripiprazole or ziprasidone which are effective in prophylaxis of mania but not depression in adults. In this way one could anticipate longer term use of an agent that might help protect against depression as well as mania, especially given the high incidence of BP-NOS converting to BP-I or BP-II upon several years of follow up. Geller et al (2012) reported that risperidone was superior to lithium or valproate in children with a BPNOS or BP I/II diagnosis. Is there an equally effective, but better tolerated atypical? Findling et al (2017) found that aripiprazole was effective in preventing mania but not depression; moreover, it was associated with considerable weight gain.

Adding lithium to an A.A. could be considered as this combination is widely endorsed for full blown manic illness (Geller et al., 2010).

A.A. in combination with lithium, or with an antimanic anticonvulsant (VPA, OXC, or CBZ) may be needed in some of the most severely affected children. Findling et al (2003) found a high rate of relapse when children with full blown bipolar disorder who were stabilized on the combination of lithium and VPA were switched to either agent as monotherapy.

7.2. More severe BP-NOS with a predominance of depression

Consider adjunctive Vit. D3, folate or N-acetylcysteine, and if history is positive for childhood adversity, consider acetyl-L-carnitine. There are positive data for children with bipolar depression (10–17) for lurasidone and for adults for quetiapine and cariprazine. Combinations of lamotrigine (LTG) with other medicines including lithium, quetiapine, and gabapentin have been positive in adults (Frye et al., 2000; Geddes et al., 2016; Van der Loos et al., 2009). Finally, family psychoeducation and skills training should be considered (Miklowitz et al., 2013, 2020; Nadkarni & Fristad, 2010).

7.3. More severe BP-NOS with prominent ultradian cycling

Davanzo et al (1999) reported a single but impressive case study of a 13 year old BP I manic child with ultradian cycling who was refractory to several years of previous treatments with lithium, atypical antipsychotics, and anticonvulsants and who remitted on nimodipine. Several groups have seen the effectiveness of nimodipine in ultra-rapid and ultradian cycling adults who have not responded to lithium (Davanzo et al., 1999; Pazzaglia et al., 1998; Post et al., 2008). These results were confirmed in individual patients using a double-blind off-on-off-design. In a series of about 50 adults with bipolar disorder in each group, the combination of nimodipine plus lithium appeared superior to lithium alone in adults (Chaudhry et al., 2010). All of these results were seen in patients not assessed for the CACNA1C gene conveying vulnerability to depression, bipolar disorder, and schizophrenia, such that the possibility of better effectiveness of nimodipine in those who are positive for this risk allele remains to be specifically studied.

The combination of lithium plus valproate (Findling et al., 2003) was much more effective than either drug alone in children with BP I disorder, and most patients required the atypical risperidone in combination with lithium or valproate for more complete response (Geller et al., 2010).

7.4. More severe BP-NOS with comorbid substance use

Adjunctive N-Acetylcysteine is effective in adults with bipolar disorder and alcohol, substance abuse or marijuana use (Berk et al., 2013), with or without a comorbid diagnosis of PTSD (Back et al., 2016). Adjunctive topiramate is effective against alcohol and cocaine use in adults, although its efficacy in youth is unclear (Delbello et al., 2005).

8. Evaluation of the interventions

The effectiveness and safety outcomes of these studies in at risk and prodromal children could be evaluated with a wide array of study designs, sequentially ranging in methodological rigor from (1) case control studies of individual children with and without high-risk syndromes who have detailed longitudinal ratings; (2) open clinical case series, preferably with comparisons with historical data; and (3) later randomized open “practical” comparative trials (Geddes et al., 2010; March et al., 2010). If systematic weekly rating by parents in the Child Network were employed (see www.bipolarnews.org; click on Child Network), these ratings and clinical experience could eventually be aggregated for case series and the results made available to the community.

In the absence of systematic longitudinal ratings by parents, a clinician could globally rate the effectiveness of each intervention on the CGI-BP Improvement Scale where: 1 or an “A” is Very Much Improved (“all better”); 2 or a “B” is Much Improved (definite clinically noticeable improvement but still symptomatic); 3 or a “C” is Minimally/Mildly Improved (some improvement but not clinically notable or worthwhile); 4 or a “D” is No Change (Similar symptoms and function as before); 5 or an “E/F” is Minimally/Much Worse (Spearing et al., 1997). Even this most minimal evaluation could allow the collation of experiences in multiple patients. In the current environment, any knowledge gleaned in clinical practice settings that would ordinarily be unavailable to other clinicians has value.

Some might argue that the generation of a formal data acquisition and analysis strategy should precede the preliminary evaluation of the type of interventions considered here. However, the availability of funding for these kinds of practical clinical trials has been minimal, suggesting that preliminary studies with less formal controls may be a more realistic starting point.

9. Maximizing treatment effectiveness and preventive effects

It is noteworthy that Birmaher et al (2009) reported that it took much longer to stabilize a child with BP-NOS than with either BP-I or BP-II. However, BP-NOS youth were less likely to relapse. Thus, the effect of treatment continuation on outcome deserves further study.

Does an extended episode of BP-NOS convey some of the same risks of recurrence as a first manic episode? After the resolution of a manic episode in an adult, consistent and multifaceted expert treatment appears indicated (Kessing et al., 2013a). Randomized treatment in a multimodal specialty clinic is more effective than standard treatment, especially for patients between 18 and 25 years of age (Kessing et al., 2013). Thus, optimal treatment for adults with syndromal BP involves a combination of pharmacotherapy and

psychoeducation – including mood charting, illness recognition and relapse prevention planning – leading to a lessening in the severity of the long term course of the illness. Further, the data of Miklowitz et al (2013, 2020) and Nadkarni and Fristad (2010) suggest similar robust results for the prodrome. Convergently, both psychoeducation and CBT are more effective when started earlier rather than later in the course of bipolar disorder.

Another indicator of the importance of concerted prevention after a first episode of mania are the data of Kozicki et al (2014) and Hu et al (2017) that cognitive deficits that occur after a first manic episode improve and are normalized in the next year only in the event that there are no further episodes during that year. Demmo et al (2017) have similar data of the adverse effects of episodes in the first year. These findings are consistent with the observations that the number of prior manic, depressive, or total episodes are related to the severity of cognitive deficits in patients assessed during euthymia (Post et al., 2012). Two episodes of depression do not increase the incidence of dementia in old age, while 4 episodes doubles the risk (Wium-Andersen et al., 2017). These data bespeak the importance of attempting to prevent illness onset at the earliest junctures to protect cognition.

It may also be important to re-consider the greater use of lithium in youngsters with prodromal symptoms as new positive findings have been observed for acute mania (Findling et al., 2015) and for preventative effects (Findling et al., 2019). Lithium has a variety of other positive effects in adults, including neuroprotection leading to increased hippocampal volume, preventing suicide and cognitive deterioration, as well as increasing the length of telomeres by direct effects on the enzyme telomerase (Post, 2017). Berk et al (2017a) found that in youngsters and adults after a first episode of mania, randomization to 1 year of lithium was superior to that of 1 year of quetiapine on all measures including mania, depression, cognition, functioning, and brain imaging abnormalities. The role of lithium for primary and secondary prophylaxis for prodromal symptoms and prevention should thus be a high priority for further study. Since lithium reverses the short telomeres in adults with bipolar disorder, one could wonder whether its use in those with childhood adversity would ultimately be sufficient to reverse the short telomeres that have been associated with childhood adversity (Epel et al., 2004), and whether such treatment would have an impact on the later manifestations of medical and psychiatric illnesses in adulthood after such adversity (Schonkoff and Garner, 2012).

10. Limitations

Concerted treatment after the first manifestations of illness is of importance in attempting to slow or reverse the high risks of episode recurrence, the development of substance abuse comorbidities (Goldstein et al., 2017; Goldstein et al., 2008), the potential for cognitive and functional deterioration, and the eventual excess in premature mortality from suicide and cardiovascular disorders (Goldstein et al., 2017; Goldstein et al., 2016). It is increasingly clear that inadequately treated bipolar disorder is a progressive illness with stresses, episodes, and bouts of substance abuse accumulating and sensitizing, likely by epigenetic mechanisms (Hoeksema and de Winther, 2016; Post, 2016; Wium-Andersen et al., 2017). Thus the efforts at early intervention prior to the development of full blown episodes that

we have outlined here deserve careful consideration even though the gold-standard data for efficacy of many of the recommendations are lacking.

Shonkoff and Gardner (2012) recommend that pediatricians become the guardians of children's psychiatric as well as physical health, especially since the experience of adversity in childhood is a risk factor for the development of multiple medical illnesses in adulthood. This recommendation would appear all the more important as the majority of children with psychiatric difficulties in the US are seen in primary care (Anderson et al., 2015). While Shonkoff and Garner (2012) and many others have made an impassioned and well-considered plea for pediatricians to take up this role, there appear to be many obstacles to its occurrence (Press et al., 2017). Better and more widely used systems to provide psychiatric support to those in primary care need to be developed. How the currently fragmented medical and psychiatric systems can be integrated and turned into a collaborative care model requires innovative solutions.

Critics of such an activist approach to early intervention and prevention in childhood onset “bipolar-like” illness are sure to argue that many of these suggestions are premature and unjustified and/or stigmatizing. These critiques occurred in relationship to efforts to study early intervention in psychosis and schizophrenia (Lieberman et al., 2019) where the early presentations are more homogeneous and consequences for long term health are severe for those who convert diagnostically. Most of these criticisms have been addressed and overcome in successful efforts to study effective approaches and develop national programs for early recognition and treatment (Galletly et al., 2016; Lieberman et al., 2019). One of the more interesting aspects of the schizophrenia prodrome studies is the very high rates of comorbid psychiatric illness which require specific treatment on their own, as the latest analyses reveal that these comorbidities are not predictive of conversion to full-blown psychosis (Alberta et al., 2018). Given the high incidence of psychiatric comorbidities in the offspring of parents with bipolar disorder (Axelson et al., 2015; Mesman et al., 2016), such an active treatment approach to comorbidities would deserve consideration for high risk children.

A further complicating factor for the exploration of potential approaches and early intervention in the bipolar realm is that a small but vocal minority even continues to argue that bipolar disorder in very young (prepubertal) children does not exist (Parry et al 2018a; Parry et al 2018b). It is noteworthy that such a passionately argued assertion does not apply to other childhood psychiatric illness, including anxiety disorders, ADHD, or any of the recently burgeoning childhood medical conditions, such as obesity, diabetes, asthma, or autoimmune diseases. It would appear that these critics of the existence of bipolar disorder in very young children should be obligated to explain what characteristics or neurobiological factors of these youngsters preclude only bipolar disorder from occurring in childhood.

We would also suggest that the argument about not stigmatizing very young children with a diagnosis of bipolar disorder is, in contradistinction, highly stigmatizing in itself (Goldstein et al., 2019). Not naming (and subsequently not properly treating) many other illnesses would be greeted with derision. The argument that a bipolar diagnosis commits one to using “strong” or “powerful” medications also would appear to have a great deal of

stigma surrounding it. Just as cancer is a diagnosis and not a “label”, and just as certain atypical findings (e.g. cervical dysplasia, dysplastic nevi) related to cancer warrant specific prevention and treatment strategies, the same can be said for bipolar disorder and other psychiatric illnesses.

Arguments against early treatment intervention also center around the observation that illness evolution following prodromal symptoms is not entirely predictable. This is clearly true, but many of the psychosocial and pharmacological interventions discussed here have polymorphous positive effects across multiple syndromes. So we would argue that in most instances, those at very high risk deserve attempts at treatment and prevention even if a bipolar diagnosis is not inevitable. The data are highly supportive of initiating some form of psychotherapy in those with depression and BP-NOS (Miklowitz et al., 2013, 2020; Nadkarni et al., 2010), although the evidence is not unequivocal (Perich and Mithell, 2019). We believe that some type of psychotherapy and/or family intervention should be part of routine for care for symptomatic at-risk children with these kinds of conditions, and is particularly indicated for youth and families who reject pharmacotherapy as their first-line treatment.

The data of Hoang et al. (2014) are particularly revealing of the magnitude of the problem of childhood onset psychiatric illness in the US. There was a 72.1-fold increase in discharge rates for the diagnosis of bipolar disorder (PBD) in youth in the United States compared to England (US, 100.9 per 100,000 population versus England, 1.4 per 100,000 population). The authors concluded: “The disparity between US and English discharge rates for PBD is markedly greater than the disparity for child psychiatric discharge rates overall and for adult rates of BD. This suggests that the difference in discharge rates for PBD may be due to differing diagnostic practices for PBD in the United States versus in England.”

We would argue that this is largely beside the point. A 72-fold increase in hospitalizations for something resembling bipolar disorder cannot be dismissed as only a diagnostic problem in the face of tens of thousands of more US than British children requiring a hospitalization for a severe behavioral disorder, whether it is bona fide bipolar disorder or not. These children – as indicated by the need for hospitalization – are clearly in need of treatment, and it is lamentable that a systematic treatment literature for children in the bipolar spectrum and related syndromes does not yet exist.

While Axelson et al (2015) found almost 75% of the children of a parent with bipolar had a major psychiatric diagnosis, it is striking that almost half (47%) of the US children of the community controls (whose parents did not have a bipolar diagnosis) received a major psychiatric diagnoses upon 7 years of prospective follow up, again revealing a high degree of childhood onset psychiatric illness in the general population in the US.

In our own sample (Post et al 2017a), more children of parents with bipolar disorder from the US had a major psychiatric problem than children of bipolar parents from the Netherlands and Germany.. The findings of high risk in children in the current generation may be an underestimate of future problems as considerable evidence supports the existence of a cohort effect for children with mood disorders and substance abuse (Post, 2016). While

Mesman et al (2016) reported no difference in the incidence of BP I and BP II diagnoses in the offspring of parents with bipolar illness from the US compared to the Netherlands, it is noteworthy that BP-NOS, which is high in the US, was not included in the analysis. Moreover, Mesman et al (2016) did find that offspring from the US had more comorbidities than those from the Netherlands.

Thus, even in the context of some diagnostic uncertainty about childhood bipolar disorder, almost all clinicians would agree that these children are ill and in need of some type concerted treatment regardless of their final diagnosis of BP-NOS, DMDD, ADHD plus ODD, or even “intermittent explosive disorder”. Regardless of the ultimate trajectory, one still needs to find out what works for which children. This cannot be done if there are not even semi-systematic treatment studies. We posit that clinicians’ best guesses about treatment based on the scanty data and rationales we have presented here deserve consideration given the magnitude of the problems associated with neglect and inaction and the potential for further difficulties because of a cohort effect (Post et al 2016a). Identifying the agents that have the most benign side effects in highest-risk or already syndromal youth should not have to wait for the discovery of definitive biological risk markers. We again acknowledge that our preliminary attempts to guide others about safety, effectiveness, and strength of rationale of a given intervention are almost certain to be controversial, but we present them with the hope that they will generate further discussion and ultimately be revised as new data become available.

11. Conclusions

Since most adult major psychiatric illnesses with high levels of lifetime morbidity begin in childhood, not attempting to alleviate the long term personal, social, medical, and financial burdens of mood, anxiety and externalizing disorders would be foolish.

The recognition of multifinality of trajectories of illness evolution can be used as an information-gathering asset, enabling a more well-powered assessment of which interventions are ultimately effective for which course patterns. Preliminary data from individual clinical experience and open comparisons can be used to better inform more rigorously controlled studies. Hudziak's principles about what is good for child development in general could be universally applied and then those who are at highest risk or already prodromal could receive more intense and targeted treatment (Hudziak et al., 2014). Such approaches would be all the more impressive given the evidence that youth who participate in music and sports programs show increased brain development and school performance (Hudziak et al., 2014). Edward Zigler, the founder of the Head Start program, believed that child health and development was a grossly neglected part of our society. Hudziak's programs are essentially a Head Start for child development and neuropsychiatric health, and could be more widely adopted in fostering children's health. The general recommendation of use in schools of mindfulness and meditation is now supported by a controlled study of mindfulness-based cognitive therapy in anxious children at high risk for bipolar disorder (Cotton et al., 2019).

Primary and secondary prevention of heart attacks and cardiovascular illness is accepted for adults; why not move these approaches earlier into childhood with many of the same recommendations applying to both bipolar disorder and cardiovascular disease, such as a very active emphasis on good diet and exercise regimens, sleep regularity, and weight maintenance strategies? Since cardiovascular risk factors are already present in children with bipolar disorder (Goldstein et al., 2017; Goldstein et al., 2016), attempts at prevention could have a dual medical and psychiatric benefit.

We hope that our encouragement to consider, employ, and evaluate treatment options will provide a fresh round of discussion and a new commitment to design and fund the necessary studies to define optimal treatment regimens for at-risk and prodromal children. Since this is not likely to happen in the near future, it would appear to us that clinicians and families with the highest risk children could begin to ask about treatment options based on extant preliminary data and assumptions about best practices. If some of the suggestions we have outlined prove to be premature and unwarranted, the subsequent efforts at intervention can then be revised accordingly. More definitive risk markers are likely to emerge in the near future, not only in the family and psychosocial domains we have emphasized here, but also from brain imaging, inflammation, circadian rhythms, endocrinology, and genetics. Linking risk markers to treatment outcomes would be facilitated by some of the preliminary efforts outlined in this article.

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Table 1

Possible interventions as a function of stage of illness evolution.

Stage	Possible interventions
I: Vulnerability/at risk	Folate 2C Vitamin D3 2C Phosphatidylcholine 2C Encourage good diet * Careful and adequate treatment of mother's depression prepartum * Adequate interventions targeting sleep/circadian rhythm stabilization across pregnancy and the postpartum period *
II: Well interval	Treatment of mothers' postpartum and later depressions * Added psychosocial support for the postpartum mother regardless of depression status * For the newborn, infant, and young child: Good diet, consistent exercise, sleep hygiene, teach ability to delay gratification * For older and school-age children: Team sports, vigorous exercise, and music lessons * For adolescents with parents with BPI or II with experience of childhood adversity: greater emphasis on, and more intensive application of, the above generic recommendations, and in addition use of group psychoeducation and family focused therapy (FFT) or its equivalent: 2B For children at high risk and are showing anger dyscontrol: facial emotion recognition training 2C 2C Acetyl-L-carnitine 2C
III: Prodrome	
A) Heterotypic prodrome (Anxiety, ADHD, ODD)	N-acetylcysteine 2B Psychotherapy/FFT 1A Stimulant (ADHD) 1B Stimulant plus alpha 2 agonist 1B Atomoxetine 2C Modafinil 2C EM Powerplus 2C Lamotrigine (Anxiety) 2C
B) Homotypic prodrome (Depression, Cyclothymia, BP-NOS)	Family-Focused Therapy or Psychoeducation 1A Omega-3-FA 2B N-acetylcysteine 2C Lurasidone 2C Other atypical antipsychotics 2C SSRIs 2C Lithium 2C
IV: Onset	
A) Stage II-IV with increased INFLAMMATION	Minocycline 2C Acetylsalicylic acid 2C Celecoxib 2C
B) For more severe BP-NOS with:	
1. Predominant MANIA	Vitamin D3 2C Folate 2C Lithium 2B Atypical antipsychotic (A.A.) 2B A.A. plus lithium 2C

Stage	Possible interventions
	A.A. plus lithium plus an antimanic anticonvulsant 2C Valproate (VPA, but not in females of child bearing age 2C
2. Predominant DEPRESSION	Vitamin D3 2C Folate 2C N-acetylcysteine 2C Acetyl-L-carnitine (if history positive for child abuse) 2C Lurasidone (especially if CRP is elevated) 2B Quetiapine 2C Cariprazine 2C Lamotrigine 2C Lamotrigine plus lithium 2C
3. Prominent ULTRADIAN CYCLING	Nimodipine (especially if patient as the CACNA1C gene) 2C Nimodipine plus lithium 2C Nimodipine plus anticonvulsant 2C Lithium plus valproate 2C
4. Comorbid SUBSTANCE USE	Adjunctive N-acetylcysteine (smoking, alcohol, cocaine, marijuana in adolescents) 2B Adjunctive topiramate (alcohol, cocaine) 2C

Possible interventions generally listed in the sequence of best-tolerated first.

UpToDate Grading 1 system: 1=strong recommendation; 2=weak recommendation;

Quality of evidence: A = high; B = moderate; C = low. (When evidence is limited to adults, quality of evidence is considered low for children.)

* = general universal recommendations