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Identifying and treating the prodromal phases of bipolar disorder and schizophrenia

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Abstract

Purpose of review—The goal of this paper is to review recent research on the identification and treatment of prodromal periods that precede bipolar and psychotic disorders. We also sought to provide information about current best clinical practices for prodromal youth.

Recent findings—Research in the areas of identifying prodromal periods has rapidly advanced. Calculators that can predict risk are now available for use during both bipolar and psychotic disorder prodromes. Cognitive behavior therapies have emerged as the gold standard psychosocial interventions for the psychosis prodrome, while several other types of therapies hold promise for treatment during the bipolar prodrome. Due to safety and efficacy concerns, pharmacologic treatments are not currently recommended during either prodromal period.

Summary—While additional research is needed to develop useful clinical tools to screen and diagnose during prodromal phases, existing literature has identified constellations of symptoms that can be reliably identified in research settings. Specialized psychotherapies are currently recommended to treat prodromal symptoms in clinical settings. They may also be useful to curtail future episodes, although further research is needed.

Keywords

bipolar disorder; schizophrenia; psychosis prodrome

Introduction

Diagnoses of schizophrenia and bipolar disorder are both preceded by a prodromal period, typically lasting months or years, in which sub-syndromal symptoms begin to manifest [1, 2]. This review discusses the current state of research in the prodromes of both schizophrenia and bipolar disorder. We focus on symptomotology and its ability to predict conversion to schizophrenia and bipolar disorder, identification of the prodrome in the clinic and possible interventions.

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Compliance with Ethics Guidelines

Conflict of Interest

Susan Conroy, Michael Francis and Leslie Hulvershorn declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Part I: Schizophrenia prodrome

Introduction to the prodromal period

The prodromal phase of schizophrenia represents a period of functional change which proceeds the onset of the first-episode of psychosis. It represents a deviation from a person's previous experience and behavior, occurring from the emergence of the first noticeable symptoms to the appearance of the first prominent psychotic symptoms. The term "prodromal" was introduced first by Mayer-Gross in 1932 [3], though the earliest studies of the phenomenon occurred in the late 1980s and early 1990s when work by researchers such as Häfner and colleagues demonstrated that schizophrenia was proceeded by the prodromal phase in up to 73% of all patients [4–7]. The prodromal phase is thought to last on average between one and five years [8] and is itself associated with not inconsequential amounts of psychosocial impairment and disability [9]. The literature often refers to individuals in the prodromal phase as at "clinical high risk" (CRH), "ultra high risk" (UHR), or having "at risk mental states" (ARMS) [10]. We will use the phrase "prodromal phase" to refer to individuals experiencing this phase.

The prodromal phase is a heterogeneous phenomenon. It is associated with depression, disrupted concentration and sleep, avolition, social isolation and even mild attenuated psychotic experiences [10–14]. Attenuated psychotic symptoms are of particular importance, as these experiences are thought to represent the later phase of the prodrome, and thus are a harbinger of transition to the onset of the first-psychotic episode [10]. Examples of attenuated psychotic symptoms include referential thinking, magical thinking, or difficulties with reality testing. Other individuals may begin experiencing poorly formed hallucinatory experiences, such as mumbled voices or brief visual hallucinations. Some individuals may act erratically, while others become anxious or withdrawn [10]. Many in the prodromal phase of schizophrenia may experience neurocognitive deficits. Meta-analyses have demonstrated diffuse, mild cognitive impairments in the prodrome, with functioning falling in between that of healthy individuals and those with schizophrenia [15, 16]. Importantly, the cognitive deficits may not only predict who is at greater risk to convert but also predict poorer psychosocial functioning [1].

Identifying the prodromal period

Over the last twenty years there has been increased focus on identifying individuals in the prodromal phase of psychosis. This can be a challenge for busy clinicians, however, considering the heterogeneity of prodromal phase presentation. Prodromal individuals who present to psychiatrists are typically help-seeking, but generally come to attention for co-occurring diagnoses rather than concern for psychosis. Frequently observed comorbid conditions include depression, anxiety, or substance use [17, 18]. Additionally, the prodromal phase of psychosis is often associated with suicidal ideation. A study by Hutton and colleagues examined the prevalence of suicidality in prodromal individuals, observing that 59% reported suicidal ideation. Furthermore, at least 47% of individuals in this cohort acknowledged having at least one suicide attempt before ultimately entering into treatment [19].

In spite of the difficulty in identifying those in the prodromal phase of psychosis, researchers have continued to make strides in refining the approach to the screening and treatment of these individuals. Estimating the prevalence of prodromal phase psychosis in the general population is difficult, as most estimates are based on patients who are presenting for treatment and may not reflect the potentially large number of individuals who do not seek help. Furthermore, treatment decisions may be complicated by the fact that of those individuals 12–35 years of age who present with signs of prodromal psychosis, only approximately 20–35% will actually go on to experience a first psychotic episode over a two-year period [20]. Current structured psychometric interviews, including the Comprehensive Assessment of the At-Risk Mental State (CAARMS) [21], the Structured interview for Psychosis-Risk Syndrome (SIPS) [22], the Basel Screening instrument for Psychosis (BSIP) [23], and the Bonn Scale for the Assessment of Basic Symptoms [24], have been observed to be consistently valid in identifying those with prodromal psychosis [20]. However, individuals identified by these instruments have only a 30–35% risk of transition to a psychotic illness over three or more years [25]. Thus, it is imperative that additional factors be incorporated into predictive models, enabling more accurate prediction of who will develop a psychotic illness. Furthermore, it is important to develop tools which are generalizable to a broader population, rather than primarily treatment seeking individuals. This type of work was recently published by Cannon et al., reporting exciting data from the second phase of the North American Prodrome Longitudinal Study (NAPS-2). This study combined not only demographic (e.g., age, family history of psychosis) and clinical data (e.g., unusual thought content, suspiciousness) but also neurocognitive (e.g., verbal learning and memory, speed of processing) and psychosocial data (e.g., traumas, stressful life events, and decline in social functioning) to generate an individualized risk calculator for psychosis which could theoretically be applied at initial clinical contact. This calculator was found to be effective at predicting conversion to psychosis at a level consistent with other predictive calculators used for cardiovascular disease and cancer recurrence risk [26]. Furthermore, since this calculator is designed to examine risk of people at the individual level it inherently accommodates the heterogeneity of individuals in the prodromal phase of psychosis. However, the authors point out that this tool is likely to be most effective in clinical trial situations. Notably, this risk calculator begins in a position assuming that an individual has screened positive for a prodromal risk syndrome. If the individual has yet to do so, the risk calculator is unusable. Importantly the authors also note that risk determinations and the ramifications of these results can be potentially confusing or distressing to patients and families, and thus these data should be explained by trained clinicians who can help patients and families understand these results [26].

An issue for clinicians who are interested in the identification of prodromal phase individuals is the length and training necessary to complete these screening measures. A review by Addington (2015) sought to examine the suitability of existing screening tools which are brief and practical instruments for initial evaluation of subjects in busy clinical settings where an in-depth assessment may not be feasible. The authors posit that to be effective and useful, a screening instrument would need to balance brevity and ease of administration with the ability to reliably distinguish those who are or are not at high risk for psychosis. 17 screening instruments were considered, with the data revealing significant

variations in key factors such as sensitivity (67–100%), specificity (39–100%), and positive and negative predictive value (24–100% and 58–100%, respectively). The authors ultimately concluded that brief screening measures are generally underexplored and require more high-quality evaluations before they can be recommended [27]. This is not to say there is no future utility in the use of these measures, but rather to call for further research into clinically useful screening devices and validation of existing scales.

Treatment

A clinical question remains after the identification of prodromal phase patients using even the most accurate of predictive tools: What is the role of treatment for the prevention of the first episode of psychosis? Proponents of treating individuals in the prodromal phase of psychosis cite not only a need to prevent or mitigate the impact of a first psychotic episode, but also the substantial amount of distress that can be seen within the prodrome itself [17]. Individuals in the prodromal phase often experience depression, anxiety, memory and attention deficits, and significant social isolation [10]. The literature demonstrates that these phenomena are associated with impaired functioning and decreased quality of life [28, 29]. The benefits of preventing the onset of psychosis seem obvious. Not only is the first episode of psychosis associated with significant disruptions in an individual's life, but for many this marks the onset of a life-long, potentially severe mental illness. Meta-analyses examining the effectiveness of prodromal phase interventions demonstrate a pooled effect indicating that treatment is successful for preventing psychosis conversion [10, 30–32]. Specifically, mean relative reductions of 64% at 6 months, 54–56% at one year, and 35–42% at 2–4 years has been demonstrated. It must be noted, however, that in spite of support for focused interventions for those in the prodromal phase, there are varying levels of support for the different treatment options [1, 10].

The best studied prodromal phase intervention is cognitive behavioral therapy (CBT). Early research demonstrated that CBT was associated with decreased symptoms, better functioning, and decreased rate of transition to psychosis [33–37]. These studies have focused on strengthening thought and behavior monitoring, schema testing, and coping skills. Newer research continues to support CBT in prodromal individuals. A study by Insing and colleagues demonstrated that CBT for prodromal phase was effective at mitigating conversion risk in the short-term and that this effect was maintained at follow-up four years later. Additionally, this studied provided evidence that CBT was associated with increased likelihood of prodromal phase remission [38]. A limitation of CBT studies is that there is heterogeneity in the CBT protocols. However, as CBT has proven successful for the treatment of symptoms associated with prodromal phase psychosis, such as depression or anxiety, much of the current literature recommends CBT as an early and safe intervention. Therefore, CBT should be offered before riskier interventions such as antipsychotic medications [10, 37].

Other therapeutic options that have been examined for the treatment of prodromal phase, include family therapy, cognitive remediation, supportive therapy, social skills training, and supported employment or education. The effectiveness of these strategies varies across trials, but generally speaking all are benign and, as such, are recommended for use prior to

antipsychotic initiation. Some investigators have attempted to offer integrated treatment models, such as the Early Psychosis Prevention and Intervention Centre (EPPIC) [39], OPUS [40] and Family-aided Assertive Community Treatment (FACT) [41]. These programs offer an array of psychotherapeutic, educational, and if indicated, medication treatment options. Important questions remain about the effectiveness of integrated treatment programs, including which services are more or less effective.

A controversial aspect of the treatment of the prodromal phase of psychosis is the use of antipsychotic medications. Though these medications may be used to treat attenuated symptoms of psychosis, they are by no means benign and it is unclear what role they may have in actually preventing a transition to psychosis. Antipsychotic medications are associated with side effects including weight gain, sedation, sexual dysfunction, and, in the long-term, extra-pyramidal symptoms [42–44]. Furthermore, it has been shown that younger individuals may be more sensitive to the metabolic effects associated with second generation antipsychotics [45], raising the question of whether or not to use these agents in the prodromal phase. There are only a handful of studies that have examined the impact of antipsychotic medication on psychosis conversion. McGorry and colleagues conducted separate studies examining the impact of risperidone plus other interventions, such as CBT and needs based intervention versus therapeutic intervention alone, finding that both groups improved functionally and symptomatically but that the effects of the risperidone were difficult to interpret [39, 46]. A trial by McGlashan et al. examined a trial of olanzapine versus placebo for prodromal phase treatment. In this study olanzapine was associated with greater symptom improvement than placebo, though both groups were associated with significant functional improvement. Additionally, the olanzapine group was associated with significantly more sedation and weight gain [47]. More recently in a multi-site study, Woods and colleagues examined the safety and efficacy of ziprasidone for preventing or delaying the onset of psychosis in 51 prodromal phase subjects. Subjects received 24 weeks of ziprasidone or placebo as well as a supportive therapy session at each research visit. The study was limited by the small sample size, which yielded only two converters in the placebo group and one in the active group. As such, the authors were not able to demonstrate an effect of ziprasidone on psychosis conversion risk. They did demonstrate an effect on attenuated symptoms of psychosis and a paucity of weight gain or ECG effects among subjects with psychosis (most of whom did not experience frank psychotic episodes)[48]. This points towards a potential role for metabolically neutral antipsychotic medications for use in those in the prodromal phase, though certainly much more research is needed in this area. At the current time the consensus on antipsychotic medications is that they are effective in treating attenuated psychotic symptoms, but should be used only when initial treatments have failed to work or when an individual begins demonstrating rapidly progressing or debilitating signs of psychosis, portending a potential psychotic break [30, 37, 49].

Not all medication studies have focused on antipsychotic use, as there have been investigations of more benign agents for conversion prevention, with the majority of work examining the role of omega-3-fatty acids. In 2010 Amminger and colleagues randomized 81 subjects to a 12-week intervention of omega-3-fatty acids (1.2 grams per day) versus placebo. They then monitored subjects for a period of 40 weeks following study termination,

examining the rate of psychosis transition as well as symptomatic and functional changes. In comparison to the study by Woods and colleagues, which was limited by the low number of converters, the Amminger study did reveal a significant effect of treatment, demonstrating a difference in cumulative risk of progression to psychosis of 22.6%. This study also demonstrated positive effects on overall symptomatology [50]. In spite of the promising initial data, subsequent studies have been less successful. A study by Nelson et al. attempted to replicate the findings by Amminger et al in a large, multi-center trial. This study randomized 304 subjects with psychosis prodrome from 10 different specialized early psychosis treatment centers. Subjects received either 1.4 grams of omega-3-FA plus up to 20 sessions of cognitive-behavioral case management (CBCM) or placebo plus CBCM. Subjects received six months of treatment and were then monitored for transition as well as symptom and functional status. The results of this trial did not replicate the initial Amminger findings, as there was no difference in transition rates between the two groups at either six or twelve-months. The authors posited that this may have been due to the lower than expected transition rate between the two groups (11% of the whole sample). Additionally, in this study both groups demonstrated significant overall symptom and functional improvement, which may have confounded results [51].

Conclusions on the schizophrenia prodrome

The literature on prodromal phase presentation, screening, and intervention clearly calls for continued research in this area. Prodromal phase screening is important, as these individuals experience distressing symptoms such as depression, anxiety, impaired concentration, and social impairments. These experiences result in disruptions in overall functioning, even in those who do not develop a subsequent psychotic illness. Existing methods to screen and diagnose individuals with psychosis prodrome have been thoroughly examined here. These tools require trained raters and are time consuming to administer, decreasing their yield in busy clinical settings. Some research has focused on brief tools for prodromal phase screening, though more work is needed in order to develop a tool that will be practical for use outside of research settings. Additionally, much more work examining prodromal phase interventions is needed. The literature is clear on the need for early intervention to prevent the transition to psychosis or to mitigate the symptoms and functional impairments associated with psychosis [1, 10, 52, 53]. The most effective means of doing so, however, have yet to be elucidated. At this point, a number of research groups have published expert consensus guidelines on psychosis prodrome intervention, highlighting a focus on early identification efforts, avoiding drugs of abuse, treating comorbid psychiatric symptoms such as depression and anxiety, and withholding antipsychotic medications until severe functional changes or psychotic symptoms occur. However, more work utilizing metabolically neutral agents, such as the Addington study with ziprasidone, would help further refine our understanding of the role of antipsychotic medication use and side effect profile.

For busy clinicians, a number of takeaway points may be gleaned from the literature. The first and perhaps most important point is to not ignore early signs of the prodromal phase. Though the field is still refining identification and predictive measures, prompt referral to experts may result in early intervention and improved long-term functioning and outcomes. Second, even if psychosis prodrome is suspected, prompt treatment of comorbid issues such

as depression, anxiety, or substance abuse should be initiated. However, one should be mindful to avoid medications with a risk of contributing to psychotic phenomenon, such as stimulant medications. Finally, clinicians should be thorough and deliberate in discussing the prodromal phase and providing education for families and patients. Alongside providing appropriate referral information, clinicians should provide clear guidance on risk and protective factors which are not only generally applicable but also relevant to each individual patient and family.

Part II: Bipolar Prodrome

Introduction: What is the bipolar disorder prodrome?

The bipolar disorder prodrome, although less studied than the psychosis prodrome, has received increasing attention in recent years. Typical age of onset for bipolar disorder is adolescence to young adulthood. The bipolar disorder prodrome comprises precursor symptoms, functional impairments, and other psychiatric diagnoses present in the months or years prior to bipolar disorder onset. Recent reviews of prospective studies have provided information about bipolar disorder precursors (affective symptoms prior to bipolar disorder diagnosis) [2] and clinical risk factors (non-affective psychopathology prior to bipolar disorder diagnosis) [54]. In a combination of hospitalized and community samples, precursors included, anxiety disorders, mood lability and mood swings, cyclothymia, subthreshold manic and hypomanic symptoms, subsyndromal depression, psychotic features in the context of depression, and early age of onset of depressive episodes [2]. In community and outpatient samples, clinical risk factors included early onset panic attacks, separation anxiety disorder, generalized anxiety disorder, conduct symptoms and disorder, ADHD, and impulsivity, with anxiety disorders being the most reliable risk factors [54].

Studies of bipolar disorder offspring are beginning to provide information about which prodromal symptoms are most predictive of development of bipolar disorder. Children of parents with bipolar disorder are at increased risk of multiple psychiatric disorders, including depressive and anxiety disorders, ADHD, oppositional defiant disorder, disruptive mood regulation disorder, and substance use disorders, as well as chronic irritability [55–57]. In several cohorts, 8–10% of offspring had developed a hypomanic, manic, or mixed episode, or frank bipolar disorder, by their mid to late teens [55, 56]. Subthreshold manic and hypomanic symptoms appear to be the best predictors of eventual, and imminent, bipolar disorder diagnosis in a cohort of over 300 high-risk offspring [55, 58]. Chronic irritability was associated with higher likelihood of bipolar disorder diagnosis [57]. Parent reports of both externalizing and internalizing symptoms, and child reports of mood lability, were predictive of conversion to bipolar disorder diagnosis [58]. Of note, the majority of high-risk offspring who went on to have a manic or hypomanic episode had a previous depressive episode and a non-mood psychiatric diagnosis (ADHD, anxiety disorder, etc.) [55].

The timing and course of the bipolar disorder prodrome is variable. Several studies have noted the prodrome onset and progression to frank bipolar disorder as gradual, rather than rapid [59, 60]. Most often, symptoms are present for several years before bipolar disorder develops, with a retrospective meta-analysis finding a mean duration of just over two years

[61]. Of note, chronic, non-episodic irritability in children, once thought to be associated with later development of bipolar disorder, is actually associated with later unipolar depression and/or anxiety disorders [62].

It is clear that the bipolar disorder prodrome does have some symptomatic overlap with the PP, and they can be difficult to distinguish clinically. One study found that obsessions and compulsions, suicidality, difficulty thinking, depressed mood, difficulty concentrating, poor energy, and mood lability were more likely to develop into mania/bipolar disorder, while subsyndromal unusual ideas were more associated with development of psychosis [60].

Tools for clinical identification of the bipolar disorder prodrome

No biomarkers have yet been validated for the bipolar disorder prodrome [63]. Several tools attempting to predict bipolar disorder have been developed, mostly based on the bipolar disorder prodrome symptoms discussed above. The Bipolar Disorder At-Risk (BAR) criteria are a set of clinical and familial characteristics thought to be highly predictive of transition from unipolar depression to bipolar disorder. They include sub-threshold mania, depression with cyclothymic features, and depression with family history of bipolar disorder [64]. These have been extended to include other risk factors, including antidepressant-emergent elation and atypical depression. Number needed to screen (NNS) in a routine clinical setting (taking into account what may or may not be recorded in a typical clinic note) has been estimated to range from 3.5 to cyclothymia to 6.9 for subthreshold mania [65]. Another tool, the Bipolar Prodrome Symptom Interview and Scale-Prospective (BPSS-P), takes 1.5 to 2.5 hours in psychiatric patients and their caregivers. So far, it has been found to be psychometrically sound but no predictive validity has yet been established [66].

A tool has been developed specifically for high-risk youth (i.e., offspring of bipolar disorder patients aged 8–17), enabling calculation of a personalized risk of developing bipolar disorder in the next 5 years [67]. It is available at http://cabsresearch.pitt.edu/calculator/BPRiskCalculator.html. Clinician administration of five different psychometric scales (measuring depression, mania, affective lability, anxiety, and global function), plus parent's age of onset, are required for the calculation.

Treatments

Both psychosocial and pharmacologic treatments have been studied in the bipolar disorder prodrome [68], as in the PP, although the amount of available evidence so far is less in the bipolar disorder prodrome. Most of these studies have been conducted in patients at high risk for bipolar disorder, usually based on family history. Clearly, the risk-benefit ratio based on current evidence favors psychosocial over pharmacologic treatment.

Psychosocial treatments—Psychosocial interventions for individuals at high risk for bipolar disorder have been reviewed recently [69]. Most of these studies involve at-risk youth and their families. Some studies provide evidence of symptom reduction, or even decreased likelihood of conversion to bipolar disorder. There are very few published RCTs in this area.

Multifamily psychoeducational psychotherapy for 8 weeks has been studied in an RCT of 9–11 year olds with depressive spectrum disorders. Transient manic symptoms were present (n=37) or absent (n=13). Over the following 18 months, 48% of patients with transient manic symptoms converted to bipolar disorder, while 12.5% of patient with only depressive symptoms converted to bipolar disorder. Treatment, compared to waitlist control, was associated with a four-fold decrease in risk for conversion (12% vs. 45%). Family history, manic symptoms, and lower overall baseline function were associated with conversion to bipolar disorder [70].

Family-focused treatment (FFT) has been tested in 9–17 year olds with mood symptoms but no bipolar disorder diagnosis, and a family history of bipolar disorder [71]. An RCT of FFT in 12 manualized sessions with patient and family showed more rapid recovery, more time in remission, and better trajectory of manic symptoms over a 1-year period in 40 patients compared to a 1–2 session psychoeducation control [72]. A multisite trial of FFT is underway currently [73].

A pilot study of Interpersonal and Social Rhythm Therapy examined high-risk 13–28 year olds with a family history of bipolar disorder and with or without personal history of psychopathology (except bipolar disorder). Of 19 participants, 13 attended at least one session of treatment. Over six months, these 13 patients attended about 50% of sessions and showed significant changes in sleep and circadian patterns (which are specifically targeted by the intervention). No changes in mood were detected [74].

A small study evaluated the effects of both individual family psychoeducational psychotherapy and omega-3 supplementation. A total of 23 patients with subsyndromal bipolar disorder symptoms (cyclothymia or bipolar disorder-NOS) were randomized to the 12-week psychotherapy intervention or active monitoring and to omega-3 supplementation or placebo (4 groups, n=5–7 each). Neither treatment significantly reduced manic symptoms compared to control; all four groups showed decreases in manic symptoms during the study. The psychoeducational psychotherapy intervention had a medium to large effect size on depressive symptoms and the omega-3 supplementation had a medium effect size on depressive symptoms. Both treatments were well-tolerated [75].

Pharmacotherapy—To our knowledge, only five studies have examined pharmacotherapies in patients at high risk for bipolar disorder. All were in children and/or adolescents with parental or strong family history of bipolar disorder, with some degree of psychopathology but no diagnosis of bipolar disorder I (also reviewed in [76, 77]). Of note, none of these studies had prevention of development of bipolar disorder as an endpoint.

The first trial of mood stabilizing medication in this population was a double blind RCT of lithium (n=17) vs. placebo (n=13) in children (average age 11) with MDD and no history of (hypo)mania, at high familial risk of developing bipolar disorder [78]. After six weeks at a therapeutic lithium level, no group differences were found on the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS). Dose-limiting side effects were problematic in this study: three of the participants in the lithium group were discontinued from treatment due to confusion/forgetfulness, and one due to nausea and vomiting.

Three studies have examined divalproex in children at high risk for bipolar disorder. In the first study [79], 24 children (average age 10) received 12 weeks of open-label divalproex. All had DSM-IV diagnoses of MDD, dysthymia, cyclothymia, or ADHD. Eighteen of 23 patients who completed the study (78%) were “much improved” or “very much improved” on the Clinical Global Impression-Improvement scale. No patients dropped out due to side effects; one patient dropped out after 2 weeks of treatment due to ongoing symptoms. In a second study of divalproex [80], high-risk children diagnosed with bipolar NOS or cyclothymia were enrolled in an RCT comparing divalproex (n=29) to placebo (n=27). Average age was 10, and patients could remain in the study up to five years. The main outcomes were time to discontinuation for any reason and time to discontinuation due to a mood event. Neither outcome differed between groups. No group differences in mania or depression symptoms, or in overall function, were found, although both groups improved over time in both symptoms and function. Divalproex was well tolerated and no patients dropped out due to side effects. In a third, pilot study of divalproex, high-risk children in an MDD episode were treated with paroxetine (n=4) or paroxetine plus divalproex (n=5) in a randomized, open-label fashion [81]. Average age was 12. The study was discontinued after enrolling 9 patients as over half of these patients developed either manic symptoms or suicidality after a mean treatment time of 22 weeks. Prominent sedation was noted among the patients in the combination therapy group.

Only one study of antipsychotics in a high-risk for bipolar disorder population exists. Twenty high-risk adolescents (mean age 14.7) were enrolled in a single-blind study of quetiapine for 12 weeks [82]. All had diagnoses of bipolar NOS, bipolar II, cyclothymia, or MDD. 15 patients completed the study (2 were lost due to nonadherence, 2 due to lack of efficacy, and 1 due to withdrawal of consent/assent). Thirteen of fifteen patients completing the study responded to quetiapine (defined as “much improved” or “very much improved” on the CGI-I). Both manic and depressive symptoms also showed statistically significant improvement. Quetiapine was well tolerated and no patients dropped out due to side effects. Patients gained an average of 0.4 kg over the study period.

A pilot study of omega-3 fatty acids combined with family psychoeducational psychotherapy (see above) found preliminary evidence of omega-3’s effect on depressive symptoms in patients with subsyndromal bipolar disorder. The supplement was well-tolerated [75].

A pharmacologic algorithm for guiding clinical care has been studied in 40 youth at high risk for bipolar disorder with depressive, manic, anxious, or ADHD symptoms for 1 year [77], but psychiatric outcomes, including development of bipolar disorder, have not yet been established. Of note, no treatment-emergent mania was detected in this study, despite the facts that 1) ADHD symptoms were treated with stimulants in some cases, and 2) antidepressants were used in patients with unipolar depression and no history of antidepressant-induced mania.

In sum, the existing literature on pharmacotherapy for prevention in individuals at high risk for bipolar disorder currently provides overall little evidence of benefit, and no study has demonstrated prevention or delay of ultimate development of bipolar disorder. Additionally,

particularly in pediatric populations, longer-term effects of mood stabilizing medications must be considered: valproate, for example, has been tied to development of polycystic ovarian syndrome and other reproductive endocrine disorders [83]. Antipsychotics (as discussed in the psychosis prodrome section above) are associated with metabolic effects including weight gain and type 2 diabetes.

Bipolar prodrome conclusions and clinical considerations

Overall, despite being a younger field than the PP, the study of the bipolar disorder prodrome has led to the identification of precursors and risk factors for bipolar disorder. The bipolar disorder prodrome is characterized primarily by anxiety disorders. Clinical tools for identifying the BPD are in early stages of development. Psychosocial interventions have shown promise in improving symptoms of the bipolar disorder prodrome and perhaps even delaying bipolar disorder onset, although more studies are needed. Mood stabilization with medications in the bipolar disorder prodrome has so far shown little utility and side effects are an important concern.

For clinicians, patients suspected of being in the bipolar disorder prodrome should be adequately treated for comorbid disorders, such as depression, anxiety, and ADHD. The possibility of treatment-emergent mania with antidepressants and stimulants should be considered, particularly in patients with a family history of bipolar disorder or subthreshold manic symptoms. Psychoeducation for families and patients is critical. These patients should be referred to available psychosocial supports, ideally those reviewed above, and carefully followed, given the high rates of suicide in emerging bipolar disorder.

Conclusion

Research is rapidly advancing in both the psychosis prodrome and the bipolar disorder prodrome, but work remains, particularly on early prospective identification and intervention. It is clear that preventative pharmacologic treatments (antipsychotics for psychosis prodrome and mood stabilizers for bipolar disorder prodrome) are not supported by sufficient evidence; however, specialized psychosocial treatments appear to have a more favorable risk-benefit ratio. In the clinic, treatment of psychiatric symptoms that prodromal patients already manifest, promotion of positive health behaviors (e.g., regular sleep, avoidance of drugs of abuse) and close clinical monitoring, is clearly indicated.

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•• Of major importance

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