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Clinical Conundrum: How do you treat youth with depression and a family history of bipolar disorder?

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Keywords

antidepressant-induced mania; family history of bipolar disorder; pediatric depression and anxiety; pharmacotherapy; psychotherapy; treatment

1 | CASE

“John” is a 14-year-old boy who presents with symptoms of depressed mood and anxiety. His mother describes him as a sociable child who participates in several extracurricular activities. However, over the past 2 years, he has become increasingly socially withdrawn. In the past 6 months, other symptoms developed, including difficulties falling asleep, academic decline, and feelings of worthlessness. During this time, John’s family reports significant psychosocial stressors: John’s brother is diagnosed with schizophrenia, and his father, who has lived with bipolar I disorder for years, is hospitalized for a suicide attempt.

Indeed, John’s symptoms significantly interfere with his social and academic functioning. With these concerns, he initially presents to his pediatrician seeking treatment for sustained depressive symptoms lasting at least 2 weeks for most of the day, every day. He shares with his pediatrician that he had been experiencing daily challenges trying to fall asleep due to low mood and worries, some anhedonia, decreased energy, difficulty concentrating in school, and psychomotor retardation. He also reports several weeks of hypersomnia, increased appetite, and eating, especially during times of stress, like studying for exams. Though he endorses passive suicidal thoughts in dark moments of hopelessness, he denies any specific plans, means, or intent to harm himself, and does not report a history of any prior suicide attempts or self-injurious behaviors.

Importantly, John denies any current or lifetime manic or psychotic symptoms. After being diagnosed with major depressive disorder, it is recommended that he receive psychotherapy to address his mood symptoms. John completes 4 months of family focused therapy (FFT) for youth at risk for bipolar disorder, after which he reported mild improvement in anxiety

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*We present a hypothetical case based on clinical encounters common in our practice. No specific patient data were presented. We have not published or submitted any related papers from this study.

but no significant improvement of his mood symptoms. His baseline and 4-month depression and mania severity scores are as follows: Children's Depression Rating Scale-Revised Raw score went from 59 to 52 and the Young Mania Rating Scale score went from 1 to 0.

Given the persistence of his mood symptoms in spite of FFT, John's therapist recommends that he speak to his pediatrician about the possibility of starting an antidepressant. After reviewing risks, benefits, and alternatives, his pediatrician starts John on 5 mg of escitalopram. Within hours, John notices that his mood had improved. However, on the third day of treatment on 5 mg of escitalopram, John's experiences increased anxiety to a level of a full-blown panic attack. While he was sitting in class, he reports suddenly feeling restless, a sense of doom, and palpitations. He worries that these intense symptoms were due to escitalopram so he discontinues the medication the next day with full resolution of his anxiety and agitation. A life chart illustrating his transition from psychotherapy to a medication trial is provided in Figure 1.

John's pediatrician refers him to a child and adolescent psychiatrist, who asks about his personal and family history of mood disorders. The child psychiatrist discovers that John's father has had a similar reaction to escitalopram, with initial rapid improvement of mood symptoms followed by anxiety, agitation, and eventually some mania-like symptoms. John's father reports that he had many subsequent manic episodes independent of antidepressant use, but his response to escitalopram was remarkably similar to what John is experiencing. His father's mood symptoms were most effectively stabilized with lamotrigine. After reviewing risks, benefits, and alternatives, John's child psychiatrist prescribes 25 mg of lamotrigine with a careful titration and close weekly follow-up. John tolerates the initial dose of lamotrigine, with eventual improvement of depressive symptoms with titrating doses and no dose-associated adverse events.

2 | DISCUSSION

This case describes an adolescent with a family history of BD presenting with depression that failed to respond to therapy and was initially treated with the selective serotonin reuptake inhibitor (SSRI) escitalopram. He had a significant adverse reaction after starting the SSRI, which may have been, in part, attributed to his familial loading for BD. This case raises the common and important clinical conundrum of how to pharmacologically treat depression in youth at high familial risk for BD, who have not yet experienced any mania symptoms.

Offspring of parents with BD have been shown to be at high risk of developing a psychiatric disorder compared to youth without any family history of BD. This is particularly true for mood disorders, as these high-risk youth can develop severe forms of depression and are susceptible to having mixed-manic symptoms as well.¹ This emphasizes the need for early intervention in this population, but treatment can often be challenging. Several case reports of high-risk patients have described adverse events to antidepressant therapy similar to those described by the patient in this case. The activation symptoms that arise temporally close to an initial dose or titration of a dose of an antidepressant suggest a disruption in the brain's arousal system. Activation is a relatively common phenomenon after starting an

antidepressant in youth regardless of a family history of BD. Activation can manifest with a broad range of symptoms such as panic-like anxiety, agitation, irritability, motor hyperactivity, impulsivity, and aggression, to more serious elevations in mood (euphoria or explosive irritability), suicidal ideation, or psychosis. There are cases in which activation symptoms may progress to treatment-emergent mania, which may indicate a high risk for conversion to BD that would warrant caution with or even avoidance of antidepressant treatment. The level of evidence for these activation and mania-like symptoms is limited to many case reports in youth and adults, retrospective cohort analyses, and one pilot randomized controlled trial that found that more than 50% of high-risk youth had significant antidepressant-induced manic symptoms after starting treatment with paroxetine.² One prospective study of 118 nine to 20-year-old youth offspring of parents with BD found that 21% of youth were exposed to antidepressants (with most exposed to either an SSRI or bupropion), of which 57% experienced an adverse event, such as irritability, aggression, impulsivity, or hyperactivity that led to discontinuation of the medication.³ Importantly, youth who were younger than age 12 were much more likely to develop an adverse reaction to antidepressants than youth over the age of 12, suggesting a developmental effect on risk. Together, these studies suggest that some offspring of parents with BD poorly tolerate antidepressant treatment. This risk emphasizes the importance of obtaining a careful psychiatric family history before starting antidepressant treatment in any youth. This careful assessment for mania in at least first- and second-degree relatives may clarify which youth might experience an adverse event versus benefit from antidepressants. Indeed, depression is a common first episode reported in individuals with BD, and antidepressants, after an initial trial or in combination with psychotherapy, remain the standard of care for treatment of depression or anxiety in youth.

Schneck et al describe initial guidelines for treating high-risk youth with depression.⁴ In high-risk patients with a family history of BD and no prior history of antidepressant-related adverse events, citalopram, escitalopram, or sertraline were recommended as first line treatments due to their shorter half-lives, compared to fluoxetine. Bupropion was also considered an acceptable non-SSRI first-line agent. In depressed high-risk youth with a history of antidepressant-related adverse events, antidepressants should be avoided, if possible, and especially in the context of a trial that achieved a therapeutic dose. In these high-risk youth, lamotrigine was recommended as first-line treatment as there is evidence of its efficacy in treating youth with bipolar depression. Quetiapine was proposed as a potential second-line treatment based on preliminary evidence. Lithium was also considered second line due to its efficacy in treating adolescents with BD-I, although there is conflicting evidence due to a negative study showing that it was not efficacious in treating depression in high-risk youth.⁴ In this study, lithium was not superior to placebo in either youth who were at risk based on a family history of BD or of multigenerational depression. Thus, it is possible that we still do not have a good answer for the efficacy of lithium in high-risk youth based on this single study. A recent randomized controlled trial suggests that in high-risk youth with subthreshold mania symptoms, aripiprazole may be an effective first-line treatment option.⁵ In this study, high-risk youth aged 5–7 who met criteria for either cyclothymia or bipolar disorder-not otherwise specified showed significant improvement in mood symptoms in the treatment compared to placebo group, but experienced some

treatment-emergent weight gain. Lurasidone may be a viable alternative given that it is the only effective and well tolerated monotherapy for pediatric bipolar depression. Likewise, olanzapine-fluoxetine may also be effective, as it is FDA approved for treating bipolar depression in youth, although it is associated with significant weight gain to the point that risk may outweigh benefit.¹ A definitive RCT to assess efficacy and safety of antidepressants for the treatment of high-risk youth with depression and/or anxiety who have no or low levels of mania symptoms is currently underway (NCT02553161).

Looking back at the case, John was started on an SSRI despite the risk of activation because alternatives, such as mood stabilizers and atypical antipsychotics, may be associated with serious side effects such as weight gain and metabolic syndrome. John experienced activation symptoms that did not progress into treatment-emergent mania symptoms, but still warranted discontinuation of the medication. The decision to start lamotrigine was based upon John's age, as lamotrigine may have a higher efficacy in adolescents compared to young children,¹ and John's father's experience with the medication, as parental response may be a predictor of the patient's response. He tolerated the lamotrigine well and noted improvement in his symptoms, but any initial positive response to subtherapeutic doses are likely attributed to a placebo effect, which has its benefits, but could also raise false hope. Hence, ongoing assessment during follow-up visits is essential to iteratively weigh benefits against risks.

This case highlights the importance of understanding how age and family history of BD can have a significant impact on treatment planning. Pending further evidence, cautious dose titration and vigilance for the emergence of treatment-related adverse events in youth at risk for BD is recommended. Further, if antidepressants are not well tolerated, understanding that alternative medications often have serious side effects of their own and discussing them with the family is essential. The current literature on treatment options is limited, emphasizing the need for further research to develop evidence-based guidelines for treatment.

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Key message

Treatment of youth with depressive symptoms should consider five issues relevant for clinical decision making: (a) age of the youth, (b) family history of BD, (c) presence of threshold or subthreshold mania symptoms, (d) prior personal and family history of response to antidepressant therapy, and (e) a careful assessment of dose-dependent clinical response to treatment and adverse events.

Learning points

- Offspring of parents with bipolar disorder are at high risk of developing mood and other psychiatric disorders, emphasizing the importance of a thorough assessment of family history.
- Clinicians should carefully assess for antidepressant related mania or other activation-like symptoms when starting an antidepressant in a patient at high risk for BD.
- There is a need for further research to assess the efficacy and safety of antidepressants in youth at risk for BD.

FIGURE 1.
 Life chart and treatment time course for patient “John.”