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EDITORIAL

Antidepressants, genetic risk, and the prevention of bipolar disorder

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The article "Medication exposure and predictors of first mood episode in offspring of parents with bipolar disorder: a prospective study," by Nery et al., highlights important concerns about the risk of future diagnostic conversion among offspring of bipolar parents.[1] At the time of inclusion in the study, the offspring did not meet criteria for a mood disorder, but over an 8-year follow-up period, 20% of the participants were found to develop a full-blown mood episode (depressive, manic, hypomanic, or mixed). Logistic regression identified baseline variables associated with increased risk of conversion, including the presence of an anxiety disorder and subthreshold mood symptomatology. Of notice, use of antidepressants was found to be associated with a higher risk of conversion, independently of the presence of subsyndromal mood symptoms.

The ability to predict (and potentially prevent) the development of full-threshold psychiatric disorders among high-risk populations has been regarded by many as the "Holy Grail" of psychiatry. In that sense, over the last decades, several cohorts of individuals at high genetic risk for bipolar disorder (BD) have been established.[2] While there seems to be a consensus as to the association between prodromal features (e.g., anxiety and subsyndromal mood symptoms) and future development of BD, results are much less consistent with regards to the possible predictive power of neuroimaging findings and other biological measures at baseline. To date, a brain signature allowing the early identification of those offspring who will later develop BD has not yet been described.

On the other hand, the association between treatment with antidepressants and increased risk for the development of BD among offspring of parents with BD has important clinical implications. Antidepressants are commonly regarded as first-choice agents in the treatment of anxiety, and may be considered the default option for patients with depressive symptoms, even in the absence of full criteria for a major depressive episode. While the potential role of antidepressants in triggering manic or hypomanic symptoms and inducing mood deregulation in patients with BD is well established, the mechanism through which these medications have the potential to impact the maturing brain among individuals at high genetic load for BD and catalyze the development of a major mood disorder is not yet clear. A meta-analysis focusing on functional neuroimaging findings among high-risk adolescents, pediatric patients with BD, and controls revealed greater activity in the right dorsolateral prefrontal cortex (DLPFC), insula, and left cerebellum among the non-bipolar offspring compared to patients with BD, who, in turn, seemed to display higher activation in limbic areas, such as the amygdala, but lower activation in the right ventrolateral prefrontal cortex and in the DLPFC when compared to controls.[3] These findings are in consonance with pathophysiological models proposing that the mood deregulation observed in BD is a result of a combination of increased limbic activity and decreased compensatory activities from frontoparietal areas.[4] Still according to this model, the increased prefrontal activity observed in unaffected offspring would be responsible for counterbalancing the increased limbic activity related to the genetic diathesis for BD, therefore preventing the development of full clinical symptoms of the disorder. Since, as pointed out by the authors, antidepressants may induce hyperactivation of limbic structures such as the amygdala, it can be hypothesized that the use of these medications in highly susceptible individuals could disturb this delicate balance and tip the scale towards the development of BD.

While there is not yet enough clinical evidence to support the routine use of mood stabilizers or antipsychotics in the treatment of offspring of bipolar parents presenting with prodromal symptoms, the decision to starting such patients on antidepressants (as well as stimulants) needs to be made with caution.[5] There is an urgent need for research focusing on possible pharmacological alternatives to the management of subsyndromal symptoms in offspring of parents with BD. Similarly, research on the

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possible role of psychosocial interventions in this population is of great interest.

Disclosure

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References

1 Nery FG, Wilson AR, Schneider MR, Strawn JR, Patino LR, McNamara RK, et al. Medication exposure and predictors of first mood episode in offspring of parents with bipolar disorder: a prospective study. Braz J Psychiatry. 2020;42:481-8.
2 Sanches M, Soares JC. Prevention of bipolar disorder: are we almost there? Curr Behav Neurosci Rep. 2020;7:62-7.
3 Lee MS, Anumagalla P, Talluri P, Pavuluri MN. Meta-analyses of developing brain function in high-risk and emerged bipolar disorder. Front Psychiatry. 2014;5:141.
4 Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. Biol Psychiatry. 2003;54:515-28.
5 Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early intervention in bipolar disorder. Am J Psychiatry. 2018; 175:411-26.