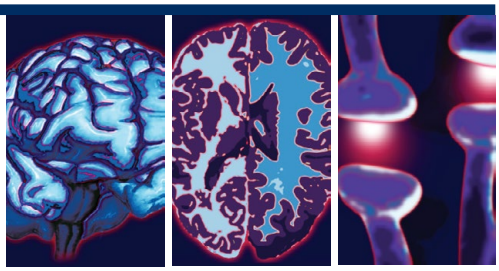
Letter To Editor



Urgent need to assess the long-term impact of the psychotropic medications on the cognitive profile among youth with bipolar disorder

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Keywords

Psychotropic medication, Bipolar disorder, Cognitive, Psychomotor, Antipsychotics

Cognitive side-effects of psychotropic medications for bipolar disorder (BD) have been widely discussed for adult patients. Basically, prospective studies suggest that long-term treatment with lithium and second generation antipsychotics (SGA) (mainly olanzapine or risperidone) may negatively affect verbal memory/learning and psychomotor speed, respectively [1-3]. Concretely, the potential negative effect of these SGA among BD patients is in contrast with their pro-cognitive properties usually observed among psychotic patients [4]. Regarding this issue, it has been postulated that SGA might have a differential effect on cognition due to specific brain alterations associated with each mental disorder [5]. For instance, one longitudinal study over two-year follow-up showed a negative association between the use of antipsychotics and cognitive functioning in BD patients, which was mediated by altered dopamine signaling in selected brain areas (e.g., prefrontal cortex), and moderation thereof by genetic sequence variation such as COMT Val108/158Met [6].

Currently, there is a great interest in the diagnosis of BD among youth. Lifetime prevalence of child and adolescent bipolar 1 disorder (BD1) is nearly 0.1%, but remarkable differences may be observed between countries, with a higher prevalence of BD not otherwise specified (BD-NOS) in the US. Concurrently, the use of lithium and several atypical antipsychotics has been approved for the treatment of adolescents with BD across countries. Specifically, the prescription of different atypical antipsychotics (risperidone, olanzapine, aripiprazole and quetiapine) is more common in the US than in other Western countries [7].

Studies addressing iatrogenic-pharmacologic effects on cognition are the exception rather than the rule among youth with BD. This is surprising for two reasons. First, because childhood and adolescence are critical periods for the cognitive development. Second, because drug-free youth with BD exhibit primary cognitive deficits (e.g., verbal/visual memory, executive functions, and social cognition) as compared with healthy controls, which are associated with poorer academic and social functioning [8]. Hence, those factors that may compromise the normative development of cognition should require in-depth assessments in general and in youth with BD specifically.

To date, most cross-sectional studies found no cognitive differences between medicated and unmedicated youth with BD [9-12]. Overall, these studies lacked of specificity because post-hoc analyses were not performed grouping medicated patients according to the type of psychotropic treatments used (e.g., anticonvulsants, atypical antipsychotics). Conversely, the only cross-sectional study assessing specific psychotropic treatments showed poorer performance on

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processing speed among BD youth using (vs. not using) antipsychotic medications [13]. The scarcity of prospective studies has not shed some light on this problem either [14,15]. Only the longitudinal study by Lera-Miguel et al. [16] reported that treatment with lithium for two years was associated with poorer development in executive control tasks (the Stroop test) among 20 euthymic adolescents with BD (90% BD1). This study also found an association between poorer development in executive control tasks (on the same test) and presence of psychotic symptoms. However, they did not report data on the possible association between the presence of psychotic symptoms and lithium treatment prescribing. It should be noted that long-term cognitive side-effects of psychotropic medications have not been addressed by prospective studies longer than three years.

Because of these limitations, there is an urgent need to carry out prospective studies which may clarify whether the psychotropic medications may negatively affect the cognitive trajectory among youth with BD. These studies should separately assess any class of anticonvulsant and atypical antipsychotics for three or more years, controlling for the effects of comorbid disorders, psychotic symptoms, duration of illness, and mood severity. Moreover, randomized controlled trials should assess the role of these psychotropic medications in cognition among youth with BD. This could help us improve the internal validity of the findings as compared with the case-control and cohort studies cited above. Additionally, quantitative data on the antipsychotic doses in chlorpromazine equivalents should also be analyzed in order to rule out cognitive impairments in a dose-dependent fashion [17,18].

When evidence was available, pharmacotherapies for BD should be chosen to minimize cognitive side-effects. Concretely, the better choice should take into account the patient-specific cognitive profile, which needs in-depth cognitive assessments at the beginning of follow-up after full clinical remission and over the follow-up period.

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