JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 19, Number 1, 2009
© Mary Ann Liebert, Inc.
Pp. 1–2
DOI: 10.1089/cap.2009.1911

Guest Editorial

Neurobiology of Pediatric Mood Disorders: Part II

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This is the second of two issues of *Journal of Child and Adolescent Psychopharmacology* with a special focus on mood disorders in youth. The overall theme of this two-part series is to highlight recent advances in the field in terms of understanding the phenomenology, the neurobiology, and the treatment of major depression, chronic irritability, and bipolar disorder (BP) in children and adolescents. This issue further extends the work published in the December 2008 issue.

Carlson et al. summarize the Research Forum that took place at the 2006 Annual Meeting of the American Academy of Child and Adolescent Psychiatry. The goal of the forum was to formulate a research agenda for early-onset BP and to improve its outcome by understanding both risk and protective factors. One of the most essential recommendations that came out of the forum was that the field needs to establish a consensus on the definition and diagnosis of BP in youth. Establishing diagnostic consensus and assessment approaches will lay the foundation for the study of genetics, biology, and treatment and will aid in the identification of mediators and moderators of early-onset BP.

In keeping with the recommendations of the research agenda outlined in the article by Carlson and colleagues, two papers (Olvera et al. and Diler et al.) focus on the assessment of youth with BP. Finding the appropriate tools to aid in the identification of children with the disorder is of significant interest given the ongoing controversy regarding the diagnosis of BP in youth and the extraordinary heterogeneity of the clinical phenotype. Olvera and colleagues tackle the critical issue of the assessment of personality traits in children and adolescents with BP. They compared temperament and character traits in youths with BP as assessed by the Junior Temperament and Character Inventory compared to healthy controls. Interestingly, they found that youth with BP had higher scores on novelty seeking, harm avoidance, and fantasy. In addition, those with BP had lower scores on other measures (e.g., self directedness, reward dependence, persistence, and cooperativeness). Their paper contributes to disentangling the differences between temperament and psychopathology in early-onset BP. However, many questions remain regarding the cart before the horse—are these personality traits due to the illness or do these personality traits predispose individuals to BP? Only future studies will help us in this regard. The paper by Diler and colleagues is equally compelling but with a different focus. These authors evaluated the usefulness of the Child Behavior Checklist (CBCL) to identify children below the age of 12 years enrolled in the Course and Outcome for Bipolar Disorder in Youth (COBY) study who had the diagnosis of BP. Prior reports indicated that the sum of attention, aggression, and anxious/depression subscales (CBCL-BPD) of the CBCL may have some specificity for pediatric BP. However, these authors found that while children with BP had more severe psychopathology than healthy controls and psychiatric controls, the CBCL-BPD phenotype was more frequently present but was not specific to BP children. This paper highlights the challenges of finding a screening tool to help aid in the diagnosis of early-onset BP.

Four papers in this issue involve the use of neuroimaging (Lopez-Larson et al., Mueller et al., Chang et al., and Dickstein et al.). Lopez-Larson and colleagues use anatomic imaging to determine if youth with unmodified *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) BP and co-morbid attention-deficit/hyperactivity disorder (ADHD) have brain-imaging findings unique to the co-morbid presentation or similar to the findings in children with BP who do not have ADHD. Interestingly, the youth with the co-morbid presentation shared neurobiologic markers with the BP alone group and did not share findings with the ADHD group, suggesting that those with BP + ADHD may not constitute a true co-morbidity but may be a subtype of BP. Mueller and colleagues assess hippocampal function using fMRI in boys with familial male precocious puberty (FMPP-excess testosterone). Boys with FMPP performed differently than unaffected controls; specifically, there were differences in hippocampal activation in response to fearful faces. This particular paper provides an elegant model for studying the influence of sex hormones on cognitive and affective brain development.

Those attending the research forum in 2006 recommended wrapping neuroimaging studies around treatment trials as a way of further assessing treatment response and adverse effects and two of the papers in this issue fulfill this research agenda. The first study is by Chang and colleagues, and it examines the effects of divalproex treatment on the structure, chemistry and function of specific brain regions in children at high risk for BP. The results of this study were essentially negative; however, despite the small sample size there was a degree of decreased prefrontal brain activation that correlated with improvement of depression. The second study, by Dickstein et al., evaluated lithium via a randomized placebo-

controlled trial in youth with severe mood dysregulation and looked at changes in magnetic resonance spectroscopy (MRS) patterns. This study is the first double-blind placebo-controlled trial completed in this particular group of children. Unfortunately, overall lithium did not significantly improve their mood symptoms, and the MRS outcome measures were negative. However, both of these wrap-around studies were likely hampered by insufficient numbers, and this highlights the need for multisite studies that combine treatment with neuroimaging in order to enhance the numbers of patients enrolled and to assure that adequate power is achieved. A multisite design would be in keeping with the recommendations that came out of the 2006 Research Forum.

Finally, there are two treatment studies and one case report included in this special issue. Pavuluri and colleagues evaluated the effectiveness and safety of open trial lamotrigine in the maintenance of manic and depressive symptoms in youths with BP. Lamotrigine was initially titrated to a therapeutic dose while the patients were stabilized on atypical antipsychotics. During the final 6 weeks, patients were on lamotrigine monotherapy. The response rates were notable for both manic and depressive symptoms, and the remission rate was 56% at the end of 14 weeks. The second study by Redden and colleagues looked at the long-term safety of divalproex ER in youth with bipolar I disorder. This was an open-label study that was 6 months in duration. The number of subjects in this study was quite substantial ($n = 226$). One hundred and nine subjects completed the study. This study fulfills at least two of the recommendations from the Research Forum in that it is a longer-term study with a large number of subjects. In general, the medication was well tolerated and the most common adverse events were weight gain, nausea, and increased appetite. Finally, a case report by Kul and colleagues, which describes maintenance lithium treatment in an adolescent, is included.

In summary, the papers in this issue provide information regarding assessment tools for the evaluation of temperament and symptoms, they provide important neurobiologic information, and add to the literature on the treatment of mood disorders. Collectively, these articles begin to tackle many of the research agenda items set forth in the Research Forum article by Carlson et al. at the beginning of this volume. We thank our colleagues for their valuable research and their important contributions to the field.