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Review

Update on the treatment of bipolar disorder in children and adolescents

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Abstract

As the phenomenology of pediatric bipolar disorder has become better delineated, clinicians are now able to more accurately assess and treat young people suffering from this condition. For pediatric patients with bipolar I disorder and symptoms of mania, medication monotherapy has been shown to lead to symptom amelioration. However, this treatment modality oftentimes does not lead to full symptom remission. In an attempt to address this observation, combination treatment strategies have recently been investigated. Recently, a maintenance study has shown that in youths who achieved remission on a combination of lithium and divalproate therapy, either of these agents alone was equally effective as a treatment strategy. In youths identified as being at genetic high risk for bipolarity who also had problematic affective symptomatology, treatment with divalproate was not found to be superior to placebo; however, those with the greatest degree of genetic risk for familial psychopathology remained in the trial longer than those with more modest amounts of familial psychopathology. These data suggest that intervention in youths with only one affected parent may not be a rational prevention strategy for pharmacological intervention in bipolar disorder, and that cohorts more genetically at risk may be a more appropriate group for preventative pharmacotherapy.
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1. Introduction

An estimated one million individuals under the age of 18 years in the US suffer from bipolar disorder [1]. However, the diagnosis and treatment of bipolar disorder in this pediatric population pose marked challenges and difficulties. Signs and symptoms of bipolar disorder may overlap with various other conditions, such as attention deficit hyperactive disorder. Furthermore, the clinical presentations of bipolar illness in the young can differ substantially from those seen in adults. The condition requires early intervention in these young patients, in order to prevent the development of physical, psychological and social consequences detrimental to the developing child or adolescent. However, in the treatment of bipolar disorder, what is known about the safety and efficacy of pharmacological agents in adults may not necessarily be applicable to children.

2. The methodology of diagnosis

Making an accurate diagnosis of bipolarity in a child or an adolescent is oftentimes a difficult task clinically. One key reason for this is the fact that bipolar disorder may present differently in children and adolescents when compared to adults [4]. To date, there is no psychometric measure that has been specifically designed to assist in the diagnosis of bipolar disorder in young people. However, the methodology of bipolar assessment in children is in evolution. Some researchers have explored the utility of the Young Mania Rating Scale (YMRS) as a diagnostic measure. The YMRS has been validated as a useful and discriminative assay that can be meaningfully interpreted in children and adolescents [17]. This was demonstrated in a study assessing 612 youths most of whom received pharmacological treatment for mood and disruptive behavioral disorders [16]. In this study, the YMRS for each youth was completed by trained raters. The youths were then stratified by diagnosis. Ratings were found to be internally consistent (alpha = 0.91). Exploratory and confirmatory factor analyses yielded a one-factor solution for boys and girls in both young (5–11 years) and older (12–17 years) sub-

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samples. As expected, the young male group achieved higher scores on several items as well as on the total YMRS score.

YMRS reporting in the hands of parents has also been established as a useful tool in distinguishing bipolar disorder from other mental health conditions [11]. Parents of 117 youths aged 5–17 years completed an adapted YMRS at an outpatient research center. Over 75% of subjects also underwent further diagnostic evaluation including a semi-structured diagnostic instrument and a clinical evaluation by a child psychiatrist. Factor analyses of the adapted YMRS suggested one dimension, with an acceptable internal consistency (alpha = 0.75). Logistic regression showed good delineation of bipolar mood disorder versus unipolar disorder, versus disruptive behavior disorder, and versus any other diagnosis [11]. Interestingly, combining the data from the parents' and clinicians' assessment does not add to the test's diagnostic ability.

3. Monotherapy in pediatric trials

Lithium has been described in numerous cohorts of young patients with bipolar disorder. In a double-blind, randomized, placebo-controlled trial, the effect of lithium was examined in adolescents (n = 25) with bipolar disorder and substance dependency [10]. Subjects were assessed for 6 weeks in an outpatient protocol, which included serum lithium levels and random urine collection in order to assess for the presence of drugs of abuse. The mean age of onset of bipolar disorder was 9.6 ± 3.9 years and the mean serum lithium levels in responders (patients scoring ≥ 65 on the Children's Global Assessment Scale [CGAS]) was 0.9 mEq/l. Patients treated with lithium showed significant improvement in outcome measures for global functioning compared with placebo (P = 0.024). As the study period was relatively brief, replication of the study with a long-term maintenance phase was recommended [10].

In a recently published open-label study, lithium was found to be effective for acute stabilization of manic symptoms [12]. A sample of 100 acutely manic bipolar I adolescents (12–18 years) were treated with lithium and examined on potential predictors of non-response, namely: the presence of prominent depressive features, psychosis, or psychiatric comorbidity. The mean age was 15.2 years, and 50% were male. Of note is that 46 of these patients were treated with a concurrent antipsychotic. Response was defined as a decline in YMRS score of ≥ 33% and a Clinical Global Impression (CGI) improvement rating of 1 or 2. Mania remission was defined as a YMRS score of ≤ 6. Overall there was substantial symptom amelioration over time. After 4 weeks of treatment, 63 patients responded to lithium and 26 achieved remission of manic symptoms. In an analysis of adjunctive antipsychotic treatment stratified for psychotic features at baseline, no differences in YMRS or CGI response rates were found in individuals with and without psychotic features. The use of the adjunctive therapy in this group, supported by the literature on bipolar I disorder in adults, suggests that combined pharmacotherapy may be a rational intervention in acutely manic bipolar patients.

Further evidence to highlight the benefits and limitations of monotherapy was provided by Kowatch et al. [13] in a head-to-head comparison of monotherapies. This was a study designed to demonstrate the effect sizes of mood stabilizers in children with bipolar I or II disorder in a mixed or manic episode. Forty-two outpatients with a mean age of 11.4 years (20 with bipolar I disorder and 22 with bipolar II disorder) were randomized to receive lithium, divalproate or carbamazepine for 6 weeks in a non-blind fashion. One definition of response was a ≥ 50% change from baseline on YMRS scores. Effect sizes were established as being 1.63 for divalproate, 1.06 for lithium, and 1.00 for carbamazepine. For the intent-to-treat population, response rates were 53% for divalproate, 38% for lithium and 38% for carbamazepine. Response rates of this magnitude illustrate that while monotherapy may be beneficial, often it is not associated with satisfactory symptom amelioration and combination therapy may be required to achieve remission in these patients. Of clinical importance is the uncertainty of which patients will or will not respond to drug monotherapy.

Preliminary evidence for the safety and effectiveness of divalproate in the treatment of bipolar disorder in youths was provided by a study in 40 patients [15]. Patients aged 7–19 years, with a manic, hypomanic, or mixed episode received open-label divalproate for up to 8 weeks. In this trial, 22 subjects (61%) showed a ≥ 50% improvement in YMRS scores during the open-label period. Significant improvements from baseline were seen for mean scores of all mania and depression rating scales ($P < 0.001$). The mean treatment effect was approximately a 12-point reduction in YMRS during open-label therapy; however, many youngsters were still not achieving full symptomatic remission at study's end.

Short-term open-label olanzapine treatment has also been shown to be efficacious and well tolerated in the treatment of acute mania in youths with bipolar disorder [8]. In an 8-week, open-label, prospective study of olanzapine monotherapy (dose range 2.5–20 mg/day), 23 bipolar youths (5–14 years old) were assessed at weekly intervals on a variety of rating scales. Olanzapine treatment was found to be associated with significant improvement in mean YMRS scores (–19.0 ± 9.2; $P < 0.001$). Using pre-defined criteria for improvement of a ≥ 30% decline in the YMRS, the overall response rate was 61%. Overall, olanzapine was well tolerated and extrapyramidal symptom measures were not significantly different from baseline, but body weight increased significantly over the study period (5.0 ± 2.3 kg; $P < 0.001$).

Comparing the response rates for olanzapine, lithium and divalproate, the literature attests that where there are drug monotherapy data, regardless of how the data are analyzed, monotherapy is associated with symptom reductions, and each agent appears to be of similar effectiveness (Fig. 1). However, many youngsters who attain benefit do not achieve full syndromal remission. The existing data that are available sug-

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