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Review

Can manic switches be predicted in pediatric major depression? A systematic literature review

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ABSTRACT

Background: The rate of switching from major depression to bipolar disorder is high in children. Predicting who is at risk for switching poses unique challenges and is of high clinical relevance. Our aim was to examine the existing scientific literature elucidating if certain clinical correlates predict ultimate bipolar switches in children initially presenting with a depressive episode.
Methods: We conducted a systematic literature search of studies assessing the risk factors for bipolar switching in youth. In all, seven studies fit our *a priori* criteria and were thus included in our qualitative review.
Results: Together, these papers found that manic switches in pediatric depression can be predicted by several risk factors, including positive family history of mood disorders, emotional and behavioral dysregulation, subthreshold mania, and psychosis.
Limitations: We identified only seven prospective informative studies for our review. The majority of subjects included in these studies were referred and Caucasian. Thus, the results may not generalize to other community samples and other ethnicities.
Conclusions: These findings can help alert clinicians of the risk of manic switches.

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Abbreviations: MDD, Major depressive disorder; SAICA, School adjustment inventory for children and adolescents

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1. Introduction

Pediatric major depressive disorder (MDD) is a prevalent, chronic psychiatric disorder associated with high levels of morbidity and disability (Carlson and Kashani, 1988; Lewinsohn et al., 1999). Epidemiologic studies show that up to 25% of youth develop MDD by the end of adolescence (Lewinsohn et al., 1998) and an additional 11% suffer from subthreshold depressive symptoms throughout their lifetime (Kessler and Walters, 1998). A longitudinal 15-year follow-up study reported that adolescent-onset MDD poses a 5-fold increased risk for suicide attempts in the follow up period and a 14-fold increased risk across the lifetime (Weissman et al., 1999). In fact, the literature documents that MDD represents the third leading cause of death via suicide among youth (Nock et al., 2013). The literature also documents that the majority of cases of juvenile onset MDD continue into adulthood (Jonsson et al., 2011), indicating that juvenile onset MDD represents a major source of morbidity, distress and disability across the lifecycle.

Because an emerging literature documents that at least half of all initial episodes of MDD in youth develop manic switches over time both with and without antidepressant treatments (Strober et al., 1993; Tondo et al., 2010; Etain et al., 2012), efforts at recognizing youth with MDD at high risk for manic switches have become paramount. In a meta-analysis of 10 trials with both adult and pediatric samples, Baldessarini et al. (2013) recently reported that the risk of antidepressant-associated manic switches was 3 times greater than the risk of spontaneous manic switches in subjects with MDD. The observed ratio of manic switches among depressed patients exposed to antidepressants was also 3 times greater in children compared to adults. Likewise, our group reported that up to half of children receiving antidepressants developed manic or hypomanic symptoms within a few months of treatment, worsening their overall prognosis (Biederman et al., 2000). Considering the high morbidity, disability, and added risk for suicide in bipolar youth (Baldessarini et al., 2013), the identification of risk factors for manic switches in youth presenting to care with a depressive episode is an area of high clinical and public health relevance.

The main aim of this study was to investigate the current body of knowledge of risk factors for manic switches in youth with MDD. To this end, we conducted a systematic literature search of all studies that addressed this issue. We hypothesized that risk factors for manic switches would be identifiable. To the best of our knowledge, this effort has yet to be undertaken in the scientific literature in pediatric depression.

2. Methods

2.1. Literature review

We performed a literature search through PubMed utilizing the following search algorithm: (bipolar depression OR bipolar disorder) AND (unipolar depression OR major depressive disorder) AND (predictor OR prodrome OR risk factors OR comparison OR switch OR conversion) AND (child* OR adolesc* OR youth). References were also reviewed and added if applicable to search criteria.

2.2. Selection criteria

We included only original prospective studies that specifically evaluated the predictors of bipolar switches in youth with depression. We defined bipolar switches as having at least one manic or hypomanic episode. We implemented the following inclusion criteria: (1) original research, (2) prospective design, (3) has operationalized assessment of major depressive disorder and bipolar disorder, (4) documents the differences in children with depression who did and did not have a manic switch, (5) subjects are limited to children under the age of 17, (6) and subjects did not have history of mania at the time of baseline assessment. Articles were excluded if they (1) were a cross-sectional design, (2) did not report on predictors of manic switches, or (3) were not written in the English language.

Two psychiatrists and a research assistant screened the articles for relevance. The screening consisted of reviewing the abstracts of the papers and excluding the papers that did not meet the *a priori* criteria. After the screening, two psychiatrists and three research assistants reviewed and identified relevant articles in full text to fully evaluate their eligibility.

2.3. Data extraction

The following variables were extracted: study sample size, proband age range, years of follow up, rate of switching from unipolar depression to bipolar disorder, and characteristics that predicted the risk of manic switches.

2.4. Qualitative analysis

We reviewed the included articles, extracting the relevant details. We also performed a qualitative analysis of the methods and results with particular note to characteristics that differentiated subjects with unipolar and bipolar depression. A meaningful meta-analysis was not able to be conducted due to the significant variability in the methods, including stratification of the sample selection and follow up of the identified papers.

3. Results

Fig. 1 shows the results of the identification of the papers. 752 papers identified from the initial database search and 25 papers identified from cross-referencing (total of 770 papers after the duplicates were removed) were screened. After screening, 45 articles were found to be relevant and the full text of each paper was carefully examined. Thirty-eight papers were excluded due to either 1) failure to report on differences in children with MDD who