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Course and Outcome of Bipolar Affective Disorder in Children

Dullur Pravin[1], Ravi Philip Rajkumar[2], Mukesh Y Prabhuswamy[3], Shoba Srinath[4], Satish Girimaji[5] & Shekhar P. Seshadri[6]

Department of Psychiatry,
National Institute of Mental Health and Neurosciences
(NIMHANS), Bangalore, INDIA.

ABSTRACT

Systematic studies of juvenile bipolar disorder have been carried out only in recent decades. Initially, Kraepelin considered bipolar disorder to be a relatively benign illness, However, recent literature suggests that bipolar disorder may present as chronic episodes with persistent deficits. Various studies, mainly naturalistic in design, have been carried out to answer questions regarding the course and outcome of bipolar disorder in children and adolescents. Indian findings differ considerably from those in Western populations. Western data suggest poor recovery from index episodes, especially in prepubertal bipolar children, longer episode duration, high rates of chronicity and rapid cycling, and a high relapse rate. Data from India, however, suggest that there is good recovery from the index episode, shorter episode duration, lower rates of chronicity, and rapid cycling. However, a higher relapse rate has been reported from Indian studies as well. The effectiveness of lithium as a prophylactic agent for childhood onset bipolar disorder needs to be reviewed.

Key words: Bipolar disorder, affective, outcome, course, children, juvenile, children

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Introduction

While bipolar affective disorder of the type classically occurring in adults characterized by discrete episodes of mania and depression with intervening periods of normalcy has been described in children since the 19th century (Kraepelin, 1899), its existence in children continued to be debated for a long time, and it was not until the later half of the 20th century that researchers in Child Psychiatry seriously began to investigate bipolar disorder in this population. Though earlier considered rare, it has since been found that the cumulative incidence in childhood and adolescence may equal the 1% rate in adults (Lewinsohn et al., 1995). In the past, children with this disorder were often misdiagnosed as suffering from completely different conditions such as attention deficit - hyperactivity disorder (ADHD), conduct disorder and childhood onset schizophrenia. This was partly due to variations in clinical presentation, but also due to the diagnosis not being considered.

Bipolar disorder has traditionally been considered to have a better prognosis than illnesses such as schizophrenia. It has been described as having a typical episodic course, with full inter - episode recovery and not leading to deterioration in personality or lasting

deficits (Kraepelin, 1899). However, others have suggested that bipolar disorder is not the regular, entirely benign form of illness that Kraepelin described. Earlier studies e.g. Hastings (1958) – which covered the entire rubric of "manic depressive illness"- showed that 15-20% of bipolar patients had an unfavourable course, and deficits could be found in up to 50% of them. Later studies confirmed these findings to varying degrees. For example, Angst (1995) found that 16% of bipolar patients had chronic episodes, and 24% had residual symptoms; Tsuang et al (1979) followed up patients up to 35 years, and showed that 22% of patients with bipolar disorder had a poor prognosis in clinical as well as social terms. In a meta-analysis of 1450 bipolar patients, MacQueen et al (2001) found that 30-60% of them had detectable psychosocial impairment. These findings suggest that bipolar illness in adults is significantly chronic and disabling, and raises the important question: does the same apply to juvenile (childhood – and adolescent onset) bipolar disorder.

Adding complexity to the issue is the relatively recent conceptualization of bipolar disorder, not as the narrow "manic-depressive" entity, but as a broad spectrum that includes bipolar II (depression with hypomania), bipolar III (anti-depressant - induced mania), cyclothymia and other "soft" disorders in addition to classical (bipolar I) illness (Akiskal, 2000). It has recently been recognized that these forms of illness are also more commonly found in children and adolescents (Akiskal, 2000; Lewinsohn, 1995). While bipolar II illness is known to be associated with more severe, prolonged depressive episodes and higher suicidality, and a distinct course (Coryell et al, 1989), it is not known if the same applies to this disorder in the juvenile population.

Therefore, there is a strong need to know about the natural history of bipolar affective disorder in all its various forms in children and adolescents. The presence of a potentially chronic, relapsing illness with possible deficits states, at a stage when the child's development towards adulthood is still in progress, could lead to potentially serious consequences. Knowledge of this could allow us to make informed statements regarding prognosis.

Finally, the management of juvenile bipolar disorder still remains an area with more questions than answers. Lithium, valproate and other agents (such as carbamazepine and atypical neuroleptics) have all been studied and found to be efficacious in treating acute manic episodes. However, the evidence regarding their usefulness in the long term prophylaxis is still insufficient. This is a question that needs to be answered before prescribing long term medications with potentially serious adverse effects in this population.

Definitions

Before starting to consider this topic, it is important to define the terms, "course" and "outcome". "Course" refers to the history of the entire illness up to a defined point in time. "Outcome" is an end-point that refers to the cross-sectional status of the patient at a given point in time. Therefore, a description of the course would include the onset of the disorder, details of the episodes and cycles, severity of the symptoms, and outcome. Three terms commonly used in designating the above are "recovery," "relapse" and

"chronicity". "Recovery" is defined as the absence of clinically significant mood symptoms in the current 8 weeks. "Relapse" refers to the emergence of significant mood symptoms after this period; and "chronicity" has been arbitrarily defined as an episode of affective illness lasting more than two years. Obviously, these parameters can be studied more effectively with longer periods of observation, but so far the longest follow-up studies in children and adolescents have lasted for no more than five years (Jairam et al, 2004; Strober et al, 1995) making prognostication about the course beyond this time period uncertain.

Study designs

Two types of study designs have generally been carried out so far in juvenile bipolar children.

1). Prospective (follow–up) studies: these studies have followed up children and adolescents with bipolar disorder at given intervals of time until a certain end-point. This has ranged from 6 months (Geller et al, 2001) to 5 years, as mentioned above. These studies provide information about course as well as outcome.

2). Retrospective studies: These studies have either been chart reviews or retrospective interviews of children and adolescents with bipolar disorder, generally the former. They tend to provide more information regarding outcome, as course cannot be reliably studied using this method.

Most of the studies have been naturalistic in design, which has its own strengths as well as weakness. On one hand, a naturalistic study allows the researcher to assess a clinical population that closely approximates outcome to a community sample, and hence is closer to ground realities. On the other hand, it does not allow us to answer questions about the effect of various medications in modifying the course and outcome. These studies have looked at the factors described above – recovery from the index episode, relapse rate, rate of chronicity, and clinical and functional outcome at end – point. They also have also attempted to find clinical and psychosocial correlates of course and outcome.

Studies in western populations:

The two largest studies carried out in the west were those of Strober et al (1995) and Geller et al. (2004). The former followed up 54 adolescent patients with a diagnosis of bipolar I disorder at 6 month intervals over a period of 5 years. They found high recovery from the index episode (96%) and an overall relapse rate of 44%, with no chronicity. They also reported quick recovery from pure mania / mixed episodes and the course was protracted if the index episode was depression. In contrast, Geller et al (2004) followed up 86 early onset patients with bipolar I & II disorder at 6 month intervals over a period of four years (mean age at onset 7.4 ± 3.5yrs). They defined 'recovery' as a period of only two weeks free of symptoms. They
found a much lower rate of recovery from the index episode (65.2%) and a higher relapse rate (55.2% at 2 years). Average episode duration was prolonged (79.2 ± 66.7 weeks). A

number of smaller studies have tended to confirm the less favorable prognosis evident in the latter study. For example, Geller et al (2001) evaluated 91 children with prepubertal or early adolescent bipolar disorder. They showed only 14.3% recovery from the index (manic or hypomanic) episode after 6 months. Findling et al (2001) studied 90 children and adolescents with bipolar I disorder aged 5-17 years. They found almost no inter episode recovery and a 50% rate of rapid cycling. Biederman et al (2004) showed only 20% functional recovery after 4 years in a study of 22 boys (aged 6-17) with bipolar disorder and co-morbid ADHD, suggesting greater chronicity in this population. A novel approach to the above was taken by Faedda et al (2004). They retrospectively studied 82 children and adolescents (age 10.6 ± 3.6 years) using Life Charting method. They found that 74% of them had psychopathology that presumably was bipolar in origin before the age of 3, consisting of sleep and mood disturbances, hyperactivity, aggression and anxiety.

Studies in NIMHANS

In contrast to the portrait painted above is the large body of work that has come from the child and adolescent psychiatry services at NIMHANS, Bangalore. The first study was carried out by Srinath et al (1998). They studied 30 subjects (age 11-16 years) with bipolar disorder (DSM III – R) at baseline and at 4 to 5 years follow – up. They found 100% recovery rates from the index episode, with rapid cycling in only 10% of patients and a relatively high relapse rate (67%). Nearly 90% of these occurred in the first 2 years. They also noted that 76% of the group comprised first episode cases. The authors suggested that this indicated a need for long term maintenance treatment in young onset bipolars. A shorter study (Rajeev et al, 2003) confirmed some of these findings. In 25 subjects aged less than 16 years, 24 (96%) recovered from the index episode over 6 months with a median time to recovery of 6 days. In a short-term study (Somashekhar et al, 1999), 20 children and adolescents (mean age 14.1 years) with mania were treated with lithium (mean dose 1125 ± 106 mg). At follow up (15 days), the recovery rate was 63.5%. Longer duration and greater severity of the episode predicted a poorer response. Jairam et al (2004) also followed up their 2003 study population every 6 months over 5 years. This revealed 100% recovery from the index episode and mean episode duration of 4.6 ± 3.9 weeks. However, 16 out of 25 patients (64%) relapsed after 18 ± 16.4 months. Of these, 11 patients relapsed despite the patient being on “adequate” treatment. Rajeev et al (2004) performed a retrospective chart review of 139 consecutive juvenile bipolars (age < 16 years), and found that 96% of them recovered from the index episode. 90% were on a mood stabilizer (usually lithium or valproate). A relapse rate of 35% (n=47) was found, with 89% of the relapses (n=42) occurring in the first two years following the index episode. Of these, 28% (n=17) relapsed despite being on adequate, “therapeutic” doses of lithium. This raises doubts about the efficacy of this drug in juvenile bipolar disorder. It must be emphasized that majority of studies in NIMHANS have been done in adolescents as opposed to Geller’s which have been done in preadolescents.

Predictors of course and outcome

Table 1

Differences between Indian and Western study populations:

Parameter	Indian studies	Western studies
Chronicity of the index episode	Low (almost 0%)	Ranges from 3.7% to 34.8%
Short-term outcome	Good (96-100% recovery in 6 months)	Poor (may be as low as 14.3%)
Rapid cycling	Less common (4%-28%)	Higher (some authors claim 100%)
Duration of index episode	Shorter (mean 4 weeks)	Longer (may be up to 79 weeks)
Relapse rate	Higher (64 to 67%)	High (44 to 55.2%)
Time to Recovery	Shorter (may be as short as 6 days)	Longer (may be up to 36 weeks)

Most of the studies referred to above have attempted to correlate various socio-demographic, clinical, psychosocial and pharmacological variables with the various parameters of course and outcome. They have yielded interesting results. Geller (2004) found only two significant correlates. Lower maternal warmth predicted an increased relapse rate, whereas the presence of psychotic symptoms predicted a higher number of weeks spent in mania or hypomania. Strober (1995) found that 60% of patients who had rapid cycling at intake had a manic or depressive episode compared to 44% of the whole sample. A further 20% had hypomania or "minor depression". Other studies have suggested that a family history of good response, presence of classical mania and having a mania - depression pattern predicted a good response to lithium. (Fristad et al, 1991; Faedda et al, 1991). Co-morbid attention deficit hyperactivity disorder and conduct disorder also predicted poorer treatment response (Masi et al, 2004), while the former has also been associated with poor long – term recovery (Biedeman et al 2004). A point of note is that western samples have reported up to 75% rates of comorbidity of disruptive behavior disorders with bipolar disorder in children (Findling et al, 2001). However,

Indian studies have shown a much lower rate of conduct disorder in bipolar children (Srinath et al, 1998). Greater baseline severity of the index episode is also a predictor of treatment non-response (Masi et al, 2004). Some authors have characterized prepubertal bipolar disorder as having a particularly malignant course at least in the short term (Geller et al, 2001). Others have not replicated this finding. Finally, with regard to the effect of treatment, Strober et al (1990) followed up 37 adolescent patients with bipolar disorder on lithium over 18 months, 13 of whom discontinued medication. This group had a threefold higher relapse rate. In both groups early relapse predicted a higher risk of later relapse. Conclusive evidence on the effect of thymoleptics in modifying the course and outcome of the disorder is lacking, though the two long term NIMHANS studies (Rajeev et al, 2004; Jairam et al, 2004) suggest that these drugs, especially lithium, may not be reliably effective in prophylaxis.

Yet another question that arises is: "When should indefinite prophylaxis be used?" Rajeev et al (2004) in their study recommended that indefinite prophylaxis be used where a family history of affective disorders was present, when child had multiple bipolar episodes or needed multiple medications for index episode or if subsyndromal symptoms were present. Other studies have not suggested recommendations for the same. Another question is: "What are the predictors of bipolarity in depressed children?" Akiskal et al (2000) suggest that paediatric onset depression is primarily bipolar. However, this view requires further investigation. Others have suggested predictors of bipolarity in depressed children. These include: rapid onset, presence of psychotic symptoms, psychomotor retardation, family history of affective disorders and drug induced hypomanic symptoms (Strober & Carlson, 1982).

Further questions

Most studies so far have looked at bipolar I disorder in children and adolescents. However, evidence (Akiskal et al, 1995; Faedda et al, 2004) suggests that other, "softer" forms of bipolarity commonly manifest in childhood and adolescence, and may later evolve into a full – blown bipolar I illness. High rates of antidepressant induced mania or hypomania (Akiskal's "bipolar III") have also been observed in this population (Pravin et al, 2004). These symptoms may occur even in the absence of overt mania or major depression once the illness is established (Stober et al, 1995). In what way does bipolar II disorder they differ in terms of course and outcome? Further, what is the effect of various medications – thymoleptics, atypical neuroleptics and antidepressants – in modifying the course and outcome of bipolar disorder? These questions need to be answered before we can claim to have sufficient knowledge of juvenile bipolarity to guide prognostication and long – term management.

Conclusions

Available evidence suggests that juvenile bipolar disorder is by no means a benign entity. Its is associated with high rates of chronicity and rapid cycling in western populations and high relapse rates, identified consistently across all studies, which suggest that the disorder is chronic, and recurrent, associated with considerable clinical and functional impairment in the long term, in spite of several authors showing excellent recovery from

index manic episodes. Given the current state of knowledge, further studies are needed to decide whether these factors can be modified in any way by pharmacological management.

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1. **Dr. Dullur Pravin**, MD **(Corresponding author)**
   Senior Resident
   Phone no. (080) 26995576
   E-mail address: dullurpravin1@yahoo.com
   Fax: +91-80-26564830 +91-80-26562121
2. **Dr. Ravi Philip Rajkumar**, MBBS
   Junior Resident
   Phone no. (080) 30910659
   E-mail address: ravi_psych@yahoo.com
   Fax: +91-80-26564830 +91-80-26562121
3. **Dr. Mukesh Y. Prabhuswamy**, MD
   Senior Resident
   Phone no. (080) 26573407

E-mail address: ypm@rediffmail.com
Fax: +91-80-26564830 +91-80-26562121

4. **Dr. Shoba Srinath**, MD
   Professor and Head of the Department
   Department of Psychiatry, NIMHANS
   Phone no. (080) 26995265
   E-mail address: shobas@nimhans.kar.nic.in
   Fax: +91-80-26564830 +91-80-26562121
5. **Dr. Satish Chandra Girimaji**, MD
   Professor
   Phone no. (080) 26995266
   E-mail address: girimaji@nimhans.kar.nic.in
   Fax: +91-80-26564830 +91-80-26562121
6. **Dr. Shekhar P. Seshadri**, MD
   Professor
   Phone no. (080) 26995268
   E-mail address: shekhar@nimhans.kar.nic.in
   Fax: +91-80-26564830 +91-80-26562121

1-6 Department of Psychiatry, Child and Adolescent Psychiatry Services, NIMHANS