Asian Journal of Psychiatry 44 (2019) 172–174

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Short communication

Lithium prophylaxis in early-onset Bipolar disorder: a descriptive study

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ARTICLE INFO

Keywords:
Bipolar
Early-onset
Adolescent
Treatment
Lithium

ABSTRACT

Subjects fulfilling DSM 5 criteria of Bipolar I disorder with onset before 18 years on Lithium prophylaxis were included. A total of 575 subjects with Bipolar Disorder were screened, 141 had early-onset Bipolar disorder, 72 patients were on Lithium and 52 provided informed consent and entered the study. Thirty-four were in the prospective group, and 18 were in the retrospective arm. Mean age at onset was 16.13 (1.40) years. About 31% (n = 16) were initiated on Lithium following first episode. Mean age at initiating lithium was 19.73 (3.82) years. Clinical profile and treatment response of early-onset bipolar disorder in the Indian context needs further study.

1. Introduction

The global prevalence of the Bipolar disorder is 2−5%, and the peak age of onset falls during mid to late adolescence (Merinkangas and Tohen, 2011). Bipolar disorder with very early-onset (< 13years) and early-onset (< 18years), have a more malignant course with poor functional outcome (Perlis et al., 2004). Nearly, 50–80% of them experience one or more recurrences in the first five years, with the recurrence risk being high in the first two years following the index episode (Pravin et al., 2005). This results in high rates of hospitalization, health service utilization, unemployment, legal problems, and poor socio-academic functioning (Geller et al., 2008; Jairam et al., 2008).

Lithium, which is among the first-line maintenance treatments for Bipolar disorder has shown to reduce recurrence, suicide and has neuroprotective effects and is generally well-tolerated in pediatric Mania (Dufy and Grof, 2018; Fountoulakis et al., 2012). There is recent evidence that early initiation of lithium increases the probability of response (Kessing et al., 2014). Recent study report that nearly 63% of Indian patients show a good response to treatment with lithium (Kapur et al., 2019). However, upto 30–37% turn out to be lithium non-responders in the Indian setting (Pravin et al., 2005; Kapur et al., 2019). There is an existing gap in evidence regarding efficacy, tolerability, and acceptability of lithium in early-onset bipolar (Dufy and Grof, 2018).

The current study examines the clinical profile of subjects with early-onset Bipolar disorder on Lithium Prophylaxis as part of treatment-as-usual. This is part of an ongoing study on genomic biomarkers in predicting prophylactic response to treatment in pediatric-onset bipolar disorder.

2. Methods

The study was approved by the Institute Ethics Committee, JIPMER and was registered with the clinical trials registry, India CTRI/2017/09/009836. Written informed consent was obtained from the parent and the patient (currently above 18 years). Assent was obtained from patients less than 18 years.

2.1. Setting

Patients attending Affective Disorder clinic of the Department of Psychiatry, JIPMER, Puducherry.

2.2. Sample

The study has a prospective and retrospective group. The retrospective arm was planned as we expected a smaller cohort in the prospective arm and possible attrition over two years follow-up.

For the prospective group patients with the diagnosis of Bipolar I disorder as per DSM 5 diagnostic criteria with age at onset of the first episode before 18 years who were started on lithium as part of treatment-as-usual and who were willing for six-monthly follow up for a minimum of 2 years after stabilization of treatment were included. For the retrospective group inclusion criteria: Patients with the diagnosis of Bipolar I disorder as per DSM 5 diagnostic criteria, with age at onset of the first episode before 18 years who are on regular treatment with lithium and on follow up for a minimum of 2 years.

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https://doi.org/10.1016/j.ajp.2019.07.053
Received 26 March 2019; Received in revised form 17 July 2019; Accepted 29 July 2019

2.3. Exclusion criteria

Comorbid Intellectual disability or autism spectrum disorder or patients with organic Bipolar disorder. In addition for the prospective group, women (> 18 years old at intake) who are planning pregnancy, currently pregnant or lactating were excluded.

Mini-International Neuropsychiatric Interview (MINI) and Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) version 6.0 were used for structured evaluation to ascertain the diagnosis of Bipolar I disorder in both arms. Non-response was defined as recurrence in the 2 year follow up while on therapeutic dose of Lithium. For retrospective arm, the Retrospective criteria of long-term treatment response in research subjects with Bipolar disorder was employed (Schulze et al., 2010) to establish non-response. Serum Lithium, Thyroid function test, Blood Urea, and Creatinine were done at baseline and six-monthly thereafter as part of routine treatment care.

3. Results

A total of 575 subjects with Bipolar disorder were screened for eligibility for participation. Of them, 141 had an onset of the first episode before 18 years. Sixty-four (45.39%) subjects were on other mood stabilizers or antipsychotics. Among them, the most commonly prescribed was valproate (n = 39, 27.6%), followed by risperidone (n = 13, 9.2%), and carbamazepine (n = 12, 8.5%). Five patients were excluded because of comorbid Intellectual disability. Of the 72 (51%) patients with early onset bipolar on lithium, 52 provided informed consent and entered the study. Thirty-four were in the prospective group, and 18 were in the retrospective group.

Of the sample, 28 were male patients, and 24 were females. Thirty-two subjects were students, n = 19 were school going, n = 5 in college, n = 8 were engaged in a semiskilled occupation; n = 6 were professionals and n = 6 were unemployed. Mean age at onset of bipolar disorder and initiation of treatment is described in Table 1. Age at onset ranged from 12 to 18 years with only one subject qualifying for very-early onset Bipolar. The mean age at intake was 22.9 (SD = 7.12) years, with a median duration of illness of 4 years. Mean years of schooling in years was 11.83 (3). The prospective and retrospective arm was comparable in terms of age at initiation of treatment, age at initiation of lithium, the total number of episodes, and the number of episodes following lithium initiation (Table 1).

In 92.3% (n = 48) patients, the polarity of the first episode was Mania, however only 6 had euphoric Mania and irritability was noted as the predominant presentation. One participant had an episode with mixed features, 12 had psychotic symptoms. With respect to number of episodes, 25% had only one episode, 38.6% had two episodes and 36.4% had more than two episodes. Family history and clinical predictors of lithium response are listed in Table 2.

The mean dose of lithium was 845.19 (178.13), and Serum Lithium was 0.796 (0.12). It was well tolerated with no adverse effects warranting a change of mood stabilizer. Renal and thyroid function test were within normal limits at baseline. During follow-up, one patient was diagnosed to have hypothyroidism (TSH-14.2).

During the maintenance phase, ten patients (19%) were on additional antipsychotic, two were on benzodiazepines, and two were on a combination of antipsychotics and benzodiazepines. Lithium was initiated following the first episode in about 30.77% (n = 16) of the sample and in 63.46% (n = 33) of participants lithium was started during the second episode.

Table 2
Frequency of clinical predictors of lithium response in early-onset bipolar disorder.

S no	Variables	N (%)
1	Manic polarity of first episode	36 (69.2)
2	Family H/o Bipolar	13 (25)
3	Family H/o good response to Lithium	10 (19.2)
4	Past H/o suicidal attempt	11 (21.2)
5	Psychotic symptoms	12 (23.1)
6	Mixed features	1 (1.9)
7	Rapid cycling	0 (0)
8	Comorbid substance use	0 (0)
9	Comorbid anxiety	1 (1.9)

As the risk of recurrence is high in the first two years, 40 (76.9%) subjects who had completed two years of treatment with lithium and on regular follow-up were examined for recurrence of an episode. Eight (20%) subjects had a recurrence. One out of 14, initiated on lithium following first episode and 7 out of 26 started on lithium later during the course had a recurrent episode. Among them non-response while on therapeutic dose was established in 4 subjects.

The profile of the non-responders although less in number was comparable to responders except that one subject had psychotic symptoms, two others required antipsychotics during the maintenance phase, two were started on lithium later during the course of illness.

4. Discussion

The mean age in this sample was 16.13 years (Table 1) indicating that majority of them had adolescent-onset as compared to western literature where more than one-third of the patients are reported to have childhood-onset Bipolar (Perlis, 2009).

First episode polarity was Mania in 69%, and this is similar to other Indian studies that have reported predominant manic polarity in both adult and juvenile-onset Bipolar disorder (Rangappa et al., 2016). The age at initiation of lithium was 3.6 years after the onset of illness, this needs to be critically reviewed, given the current evidence favoring early initiation of lithium (Kessing et al., 2016). Time to arrive at a diagnosis of bipolarity may be delayed because of atypicality in clinical presentation in early-onset Bipolar. It is known that typical symptoms increase with age and severity and initial episodes are often amorphous in presentation and comorbidities complicate the clinical presentation (Jairam et al., 2008; Kandasamy et al., 2016).

Among those receiving diagnosis of Bipolar in the first episode, the clinical predictors of response to lithium such as polarity of first episode, presence of euphoria, family history of response, absence of psychotic symptoms, substance abuse and rapid cycling (Ayano, 2016), often employed in clinical setting may not favour administration of lithium in many patients with paediatric bipolar (Table 2). In this sample, there were fewer participants if any with mixed features, rapid cycling or substance abuse, and about ten (19.2%) subjects had psychotic symptoms in contrast to western literature. Very few (n = 6;

Table 1
Clinical profile of early-onset bipolar disorder.

Clinical profile of EOBD	Prospective (n = 34) Mean (SD)/n (%)	Retrospective (n = 18) Mean (SD)/n (%)	Total (n = 52) Mean (SD)/n (%)
Mean age at onset of Bipolar disorder (years)	16.26 (1.330	15.89 (1.53)	16.13 (1.40)
Mean age at initiation of medications for Bipolar (years)	17.29 (2.44)	18.11 (3.83)	17.58 (2.99)
Mean age at initiation of lithium (years)	19.91 (3.90)	19.39 (3.74)	19.73 (3.82)
Mean number of episodes (lifetime)	2.53 (1.9)	2.78 (2.18)	2.6 (1.98)
Number of episodes after starting Lithium	0.44 (1.73)	1.11 (2.4)	0.61 (2.02)

11.5%) had classical euphoric Mania in contrast to adult onset Bipolar; however, the presence of irritable Mania did not determine non-response to lithium.

It is however essential to clarify that this sample constitutes only 51% of those with early-onset Bipolar disorder as it included only subjects on lithium prophylaxis. Patients with atypical features could have received Valproate or other mood stabilizers whose data is unavailable as part of this study. Future studies examining and comparing the clinical profile, response, and tolerability to various mood stabilizers in early-onset Bipolar disorder may be indicated in our setting. This will help address high rates of recurrence and poor functional outcome affecting the developmental and socio-academic trajectory of these adolescents. As the peak incidence typically coincides with the secondary and higher secondary board exams in the Indian setting with the negative long-term academic outcome, early prophylaxis may also have unique relevance to the Indian setting.

One of the significant concerns in prescribing lithium is the variability in response. Though the sample is small in this study, a subset turned out to be partial responders and non-responders, and this is in line with earlier studies which have reported that about 30–37% turn out to be non-responders (Pravin et al., 2005; Bellivier and Marie-Claire, 2017; Kapur et al., 2019). Given the current lack of predictability of response, it needs careful risk-benefit evaluation and facilitation of informed decision making by the parents (Kandasamy et al., 2016). Considering the ethical concerns in justifying a trial of lithium for young patients with Bipolar disorder identifying predictive biomarkers is necessary to improve the prophylactic management of early-onset bipolar (Bellivier and Marie-Claire, 2017). While this is still underway, the decision of early initiation is an option that clinician should provide families given the current evidence and recurrence risk.

5. Limitations

The study has a relatively small sample size and included both a prospective and retrospective sample. As subjects on other mood stabilizers were excluded, there were limitations in comparing clinical profile and the response of patients on different mood stabilizers. The study employed MINI/MINI KID version 6.

6. Conclusion and future directions

The clinical profile of early-onset Bipolar disorder in the Indian setting may differ from western literature in terms of clinical presentation, comorbid patterns and therefore, treatment response. Currently, there are limitations in predicting non-response to lithium clinically. Identifying genomic biomarkers may help predict treatment response to lithium and plan personalized care for young people with this disorder in the early course of illness, given its unique properties. More research from Indian context examining the safety, tolerability including neuro-cognitive effects of mood stabilizers among youth with early-onset Bipolar disorder is warranted.

Declaration of competing interest

None.

Funding agency

Funded by the Science and Engineering Research Board (SERB), a statutory body of Department of Science and Technology, Government of India (File No. ECR/2016/001849).

Acknowledgement

We would like to acknowledge the contribution of (late) Prof Steven A Dkhar, Professor of Pharmacology, and (late) Dr Surendiran Adhitan, Associate Professor of Pharmacology, JIPMER.

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