Effect size of lithium, carbamazepine, and sodium valproate in child and adolescent bipolar 1 disorder during manic phase: A prospective open-label study

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Aim: The aim was to evaluate the “effect size (ES),” tolerability, and acceptability of lithium, carbamazepine, and sodium valproate in the acute phase treatment of pediatric Bipolar 1 disorder patients during manic phase. Materials and Methods: This hospital-based, prospective, open-label study included 67 patients in manic phase of bipolar I disorder, aged 6–17 years, after informed consent by the caregivers. The patients were randomly assigned to the lithium group (n = 30), carbamazepine group (n = 20), and sodium valproate group (n = 17). They were assessed with the Schedule for Affective Disorders for School Age Children’s-Present and Life time version administered to the parent and child separately, Conner’s Abbreviated Rating Scale, and Cassidy Scale for Manic States (CSMS). Lithium was started in the dose of 30 mg per kg of body weight, carbamazepine in the dose of 10–20 mg/kg/day, and sodium valproate in the dose of 10–20 mg/kg body weight. Antipsychotic (chlorpromazine [CPZ] 100–500 mg per day or haloperidol up to 750 mg of CPZ equivalent) was allowed in the study. Injection haloperidol 10 mg and injection promethazine 50 mg intramuscular were allowed for initial 3–5 days to combat acute agitation. Rescue medication such as injection lorazepam 2–4 mg intramuscular was allowed throughout the study duration. The patients were rated weekly on CSMS, Bipolar Clinical Global Impression, Udvalg for kliniske Undersogelser Side Effect Rating Scale, and side effect checklist for lithium, sodium valproate, and carbamazepine, respectively. The serum level of concerned drug was obtained at weekly intervals and dose hiked, if needed to get target serum level. Results: The response rate was 90% in lithium group, 70% in carbamazepine group, and 88% in sodium valproate group on the basis of ≥33% reduction from baseline CSMS. The effects of change of CSMS over the 6 weeks across the three treatment group were found to be highly statistically significant. Conclusions: In the acute phase treatment of pediatric bipolar 1 disorder patients during manic phase, the ES for lithium was 0.85, for carbamazepine 0.71, and for sodium valproate 0.84. These agents are well tolerated in treating bipolar disorder in children.

Keywords: Bipolar disorder in children and adolescents, carbamazepine, effect size, lithium, sodium valproate, tolerability, typical antipsychotic

It has been reported that when patients recalled their first mood episode, approximately 65% of adults experienced adolescent bipolar disorder (BD) was described by Kraepelin who noted a significant emergence of BD at puberty.[1] Once thought to occur only rarely in youth, BD is now estimated to affect 1% of children and adolescents.[2]
onset of symptoms prior to the age of 18, while 27.7% experienced their first mood episode before the age of 13 years.[6] An estimated 30%–40% of the child and adolescent psychiatric hospitalization are due to BD.[4] There is growing evidence that early mood disorders are widespread, recurrent, and often chronic, increasing the risk of lifelong disability.[5] Children and adolescents with BD have significantly higher rates of morbidity and mortality as compared to healthy children. In addition, the disorder results in impaired social, family, and academic functioning, resulting in reduced quality of life.[6] Pediatric BD disrupts the normal development of children and adolescents.[7] The developmental variations in presentation, symptomatic overlap with other disorders, and lack of clinician awareness have all led to underdiagnosis or misdiagnosis in children and adolescents.[8]

Effect size (ES) is a name given to a family of indices that measure the magnitude of a treatment effect. Unlike significance tests, these indices are independent of sample size. EZ measures are the common currency of meta-analysis studies that summarize the findings from a specific area of research.[9] There is a wide array of formulas used to measure ES. In general, ES can be measured in two ways: as the standardized difference between two means, or as the correlation between the independent variable classification and the individual scores on the dependent variable. This correlation is called the “ES calculation.”[10] ESs can also be thought of as the average percentile standing of the average treated (or experimental) participant relative to the average untreated (or control) participant. An ES of 0.0 indicates that the mean of the treated group is at the 50th percentile of the untreated group. An ES of 0.8 indicates that the mean of the treated group is at the 79th percentile of the untreated group. An ES of 1.7 indicates that the mean of the treated group is at the 95.5th percentile of the untreated group. ESs can also be interpreted in terms of the percent of nonoverlap of the treated group’s score with those of the untreated group. An ES of 0.0 indicates that the distribution of score for the treated group overlaps completely with the distribution of scores for the untreated group; there is 0% of the nonoverlap. An ES of 0.8 indicates a nonoverlap of 47.4% in the two distributions. An ES of 1.7 indicates a nonoverlap of 75.4% in the two distributions.

Despite advances in the understanding of the symptomatology and phenomenology of BD in children and adolescents, there remains a dearth of information regarding pharmacotherapy for BD. Current practice parameters are based on limited evidence and/or studies using adult patients. General guidelines indicate that it is important for young patients with BD to continue treatment for an extended period of time in order to manage the frequent relapses of childhood-and adolescent-onset BD.[6,11] There is a paucity of systematic studies on the efficacy of mood stabilizers for prepubertal BD. This is a priority area given the morbidity and chronicity of this disorder. Studies of mood stabilizers for BDs are few, are small, and have used heterogeneous inclusion/exclusion criteria, making it difficult to know for which populations this approach is useful. Because such disorders are relatively intractable, this area deserves more study. In addition, comparative studies examining the efficacy of these agents, including time to response, have not been undertaken. Given data that valproate may have a quicker onset of action than lithium in bipolar adults and that it can be given in a rapid loading strategy, comparison of active treatments in adolescent BD might permit more rational treatment strategies.[12,13] Systematic assessment of frequent and infrequent side effects of these compounds in children with psychiatric disorders is also needed. Existing data in the literature do not completely address side effects that may be more frequent in pediatric psychiatric populations. The present study is an attempt to give a better insight into the psychopharmacological treatment by evaluating the “ES” for lithium, carbamazepine, and sodium valproate in the acute phase treatment of bipolar 1 disorder patients during a manic phase and to ascertain the tolerability and acceptability of these three mood stabilizers in the child and adolescent population.

MATERIALS AND METHODS

This hospital-based, prospective, open-label study was conducted at the Department of Child and Adolescent Psychiatry, Central Institute of Psychiatry, Kanke, Ranchi, a tertiary care postgraduate teaching institute. It has a total bed capacity of 643, out of which 18 beds are for the Department of Child and Adolescent Psychiatry. The study protocol was approved by the Institutional Ethical Committee.

Sample

Samples were collected using purposive sampling method from inpatients of the Child and Adolescent Psychiatry ward.

Inclusion criteria

1. Patients meeting Diagnostic and Statistical Manual of Mental Disorder-IV Text Revision (TR) diagnostic criteria for BD 1 during a manic episode[14]
2. Age between 6 and 17 years
3. Score >15 on Cassidy Scale for Manic States (CSMS)[15]
4. Informed consent by caregivers, i.e. parents or major first-degree relatives.
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Exclusion criteria
1. Current medical or neurological conditions requiring treatment
2. Mental retardation judged by academic performance
3. Current or lifetime diagnosis of schizophrenia, autism, attention deficit hyperkinetic disorder (ADHD), obsessive compulsive disorder, depression and anxiety disorder
4. Substance abuse within the last 6 months
5. Use of psychotropic medicines within the last 2 weeks including narcoleptics, stimulants, and antidepressants
6. One month drug free if on depot antipsychotic.

Tools for assessment

Sociodemographic and clinical data sheet
It contained questions about age, sex, religion, informant, address, past history, family history, total number of episodes, and development history, which was filled up after a detailed interview with the patient and the caregiver.

Schedule for Affective Disorders for School Age Children’s-Present and Life time version
This was administered to the parent (usually the mother) and child separately. This tool was used for screening and to make the diagnosis. Apart from the current diagnosis, Schedule for Affective Disorders for School Age Children’s-Present and Life time versions (K-SADA-PL) also gives the lifetime diagnosis.[16]

Conner’s Abbreviated Rating Scale
The scale was developed by Conner to evaluate and diagnose ADHD. The items are rated on a 0–3 point scale. This study used the teacher version. It was used to exclude comorbid diagnosis of ADHD.[17]

Cassidy Scale for Manic States
The scale was used to assess the manic along with the mixed features on a 0–5 point scale. This consists of 20-point scale.[18]

Bipolar Clinical Global Impression-Bipolar versions
This is a 3-point scale which measures illness severity, global improvement, and therapeutic response. Each item on the Clinical Global Impression (CGI) is rated separately, and there is no overall score. The CGI is designed to be useful in situations in which changes over time have to be assessed.[19]

Side effect checklist for lithium, sodium valproate, and carbamazepine
This checklist was used to assess the side effect of lithium, sodium valproate, and carbamazepine separately.[19]

Udvalg for Kliniske Undersogelser Side Effect Rating Scale
This scale gives a comprehensive assessment of side effect related to antipsychotic use in four categories – psychic, neurologic, autonomic, and others. It also gives a global assessment of the interference by the existing side effects with the patient's daily performance and its consequences on treatment regimen.[20]

Procedure
Patients were taken from the Department of Child and Adolescent Psychiatry with a diagnosis of BD 1 current episode-mania or mixed. Their parents were explained about the study, and written informed consent was obtained. They were allotted randomly to a naturalistic open-label study design of 5 weeks to lithium, carbamazepine, and sodium valproate group.

A detailed physical examination was done to rule out any physical illness. Laboratory testing for complete hemogram, blood urea, serum creatinine, liver function test, thyroid function test, and electrocardiogram was done. Dosage of the drug and their serum level was monitored at the 1st, 2nd, 3rd, 4th, and 5th weeks of the treatment. The primary efficacy measures were the weekly CGI-Bipolar version (BP) on improvement subscale and CSMS.

Drug schedule
Lithium was started at a dose of 30 mg per kg of body weight.[21] The target serum level was 0.8–1.2 mmol/L.[22] Carbamazepine was started at a dose of 10–20 mg/kg/day (200–600 mg/day). The target serum level was 8–12 µg per liter.[23] Sodium valproate was started at a dose of 10–20 mg per kg of body weight. The target serum level was 85–110 µg per liter.[24]

Daily dosages were usually divided into twice-daily or thrice-daily schedules.[25] The medication such as injection lorazepam 2–4 mg intramuscular was allowed throughout the study duration.

The treating team was allowed to use tablet chlorpromazine (CPZ) at a dose of 100–500 mg per day or tablet haloperidol at a dose of 5–15 mg per day. Injection haloperidol 10 mg and injection promethazine 50 mg intramuscular were allowed for initial 3–5 days to combat acute agitation at the time of admission.

Assessment
At the time of admission, both patients and parents were interviewed. Information was gathered and sociodemographic datasheet was filled up. K-SADS-PL, CARS, and Baseline Ratings on CSMS were done. Patients were rated weekly on CSMS; CGI-BP; side effect checklist for lithium, sodium valproate, and carbamazepine; and Udvalg for Kliniske Undersogelser (UKU) Scale. Serum level of concerned drug was obtained and dose hiked, if needed to get target serum level.
Statistical analysis

Statistical analysis was done with Statistical Package of Social Sciences (SPSS) – version, 13.0 (SPSS13; IBM, Chicago, USA). To find out the group differences of the clinical variables having categorical data, the Chi-square test was used. Post hoc test was done using least significant difference (LSD) model because there was no significant difference with the use of other post hoc test models. Multivariate tests were done to show the multiple comparison across the three treatment groups using CSMS and CSMS versus lithium carbonate, carbamazepine, and sodium valproate group. Responders were classified as ≥33% reduction in CSMS or CGI-BP score of 1 or 2 in improvement subscale. ES was calculated by first calculating Cohen’s “d,” which is calculated as difference in sample mean divided by their common standard deviation. Tolerability and acceptability of lithium, carbamazepine, and sodium valproate were assessed using the side effect checklist to show the percentage of side effect across the three groups. P = 0.05 was used throughout the analysis.

RESULTS

A total of 67 children and adolescent patients with Bipolar I disorder participated in this study after each caregiver gave informed consent. The patients were randomly assigned to lithium group (30 participants), carbamazepine group (20 participants), and sodium valproate group (17 participants). Out of a total of 67 patients, only 37 patients completed the 6 week study protocol, which included 20 in the lithium group, 9 in the carbamazepine group, and 8 in the sodium valproate group. The major reason for reduced level of participation during the initial week was the change of treatment regimen (e.g. use of electroconvulsive therapy or change of antipsychotic) due to patient being restless and aggressive, whereas the dropouts during later weeks were due to early discharge of the patients. Intent-to-treat analysis was done on the basis of Last Observation Carried Forward (LOCF) method for the patients who completed at least 1 week of the study (n = 67). LOCF method is an established method for substituting missing values in longitudinal studies.

There was no statistically significant difference in the demographic and clinical variables in the three groups, indicating that the three groups were homogenous [Tables 1 and 2]. There was a statistically significant difference with the use of lithium in patients with a family history of affective disorders (P = 0.034). There was no significant difference with the use of carbamazepine in patients with any of the variables. The number of patients receiving sodium valproate reached statistically significant difference with the total number of episodes (P = 0.021) and past depressive episodes. There was also a statistically significant difference (P = 0.007) among the patients receiving sodium valproate with the number of past depressive episodes [Table 3].

Comparison of CSMS scores across the three treatment groups showed a marked reduction in the score of CSMS in the 2nd week in all the three groups with a worsening in the 4th week in lithium and carbamazepine group, but the difference was not statistically significant [Table 4]. Comparison of reduction in CSMS scores across the three treatment groups showed a marked reduction from the 1st to 3rd week in all the three groups. The reduction in CSMS scores across the three treatment groups was statistically significant at the 2nd week (P = 0.045), 4th week (P = 0.014), and 5th week (P = 0.043) [Table 5]. Table 6 shows the dose of mood stabilizer (mg/day) across the three treatment groups. Comparison of UKU total score wise across the three treatment groups did not show statistically significant difference over the 6 weeks [Table 7]. Comparison of dose of trihexyphenidyl (mg/day) across the three treatment groups showed that it reached a statistically significant difference at the 1st week in the lithium group [Table 8]. The frequency of dystonia experienced by the patients across the three groups in the initial 3 weeks of the study is shown in Table 9. At the 1st week, lithium group experienced the highest number of dystonia.

Table 10 shows the post hoc test using LSD model of requirement of mean antipsychotic (CPZ equivalent) dose and CSMS change from baseline to end of the study using multiple comparisons across the three treatment groups. LSD model was used because there was no significant difference across the three groups when other post hoc test models (such as post hoc Scheffe model) were used. There was a statistically significant difference between requirements of antipsychotic in carbamazepine group as compared to lithium group (P = 0.014). The table also showed a statistically significant difference in CSMS change from baseline to end of the study when multiple comparisons were made between carbamazepine and sodium valproate group (P = 0.059).

It can be seen from Table 11 that the time required for getting therapeutic lithium level is 2nd week, 1st week in carbamazepine group and 3rd week in case of sodium valproate. The therapeutic serum level of lithium was 0.8–1.2 mmols per liter. The therapeutic carbamazepine serum level was 8–12 µg per liter. The therapeutic sodium valproate serum level was 85–110 µg per liter.

The effect of change of CSMS scores over the 6 week across the three treatment groups was found to be significant at 0.000 level. The effect of the change of
Table 1: Sociodemographic details of the sample and comparison across the three treatment groups

| Variables                        | Lithium (n=30), n (% ) | Carbamazepine (n=20), n (% ) | Sodium valproate (n=17), n (% ) | df | χ² | P    |
|----------------------------------|------------------------|------------------------------|---------------------------------|----|----|------|
| Sex                              |                        |                              |                                  |    |    |      |
| Male                             | 16 (53)                | 14 (70)                      | 13 (76)                         | 2  | 2.94 | 0.22 |
| Female                           | 14 (47)                | 6 (30)                       | 4 (24)                          |    |    |      |
| Religion                         |                        |                              |                                  |    |    |      |
| Hindu                            | 24 (80)                | 16 (80)                      | 14 (82)                         | 2  | 0.04 | 0.97 |
| Muslim                           | 6 (20)                 | 4 (20)                       | 3 (18)                          |    |    |      |
| Education                        |                        |                              |                                  |    |    |      |
| Illiterate                       | 1 (03)                 | 3 (15)                       | 2 (12)                          | 6  | 8.41 | 0.20 |
| Primary                          | 12 (40)                | 5 (25)                       | 2 (12)                          |    |    |      |
| High school                      | 17 (57)                | 11 (55)                      | 13 (76)                         |    |    |      |
| Senior secondary                 | 0                      | 1 (05)                       | 0                               |    |    |      |
| Number of past manic episodes    |                        |                              |                                  |    |    |      |
| Nil                              | 26 (87)                | 16 (80)                      | 11 (66)                         | 6  | 8.96 | 0.17 |
| One                              | 3 (10)                 | 3 (15)                       | 3 (17)                          |    |    |      |
| Two                              | 1 (03)                 | 0                            | 3 (17)                          |    |    |      |
| Three                            | 0                      | 1 (05)                       | 0                               |    |    |      |
| Number of past depressive episodes|                       |                              |                                  |    |    |      |
| Nil                              | 22 (73)                | 16 (80)                      | 15 (88)                         | 2  | 1.47 | 0.47 |
| One                              | 8 (27)                 | 4 (20)                       | 4 (22)                          |    |    |      |
| Family history                   |                        |                              |                                  |    |    |      |
| Nil                              | 14 (47)                | 13 (65)                      | 10 (59)                         | 4  | 5.96 | 0.20 |
| Affective illness                | 15 (50)                | 4 (20)                       | 6 (35)                          |    |    |      |
| Nonaffective illness             | 1 (03)                 | 3 (15)                       | 1 (06)                          |    |    |      |
| Type of onset of index episodes  |                        |                              |                                  |    |    |      |
| Abrupt                           | 9 (30)                 | 8 (40)                       | 12 (70)                         | 4  | 8.84 | 0.06 |
| Acute                            | 17 (57)                | 11 (55)                      | 5 (30)                          |    |    |      |
| Insidious                        | 4 (13)                 | 1 (05)                       | 0                               |    |    |      |
| Total number of episodes (including index episodes) | | | | | |
| One                              | 20 (67)                | 14 (70)                      | 10 (59)                         | 6  | 7.65 | 0.26 |
| Two                              | 7 (23)                 | 5 (25)                       | 3 (18)                          |    |    |      |
| Three                            | 3 (10)                 | 0                            | 4 (23)                          |    |    |      |
| Four                             | 0                      | 1 (05)                       | 0                               |    |    |      |
| Antipsychotic drug               |                        |                              |                                  |    |    |      |
| CPZ                              | 21 (70)                | 15 (75)                      | 16 (94)                         | 2  | 3.74 | 0.15 |
| Haloperidol                      | 9 (30)                 | 5 (25)                       | 1 (06)                          |    |    |      |

df – Degree of freedom; χ² – Chi-square value; P<0.05; CPZ – Chlorpromazine

CSMS scores was compared over the 6 weeks with lithium carbonate, carbamazepine, and sodium valproate groups using repeated-measures ANOVA. The results were not found to be statistically significant (P = 0.296). Partial Eta square value is an indirect evidence of the ES of the group [Table 12]. Table 13 shows the percentage of responders on the basis of CGI change score of 1 or 2 or a ≥33% reduction in baseline CSMS. Sodium valproate group had the highest responders on the basis of CGI change Score of 1 or 2 and lithium group had the highest responders on the basis of ≥33% reduction in baseline CSMS. When the mean of the two response variable was taken into consideration, sodium valproate group showed the highest response rate of 85%. Lithium had the highest ES of 0.85 followed by sodium valproate with an ES of 0.84 and carbamazepine having ES of 0.71. Thus, lithium and sodium valproate were said to have a large ES (>0.8%) whereas carbamazepine had medium ES (>0.7%) [Table 14].

The most common side effect on lithium carbonate was tremor (38.76%) followed by thirst (28.90%), dry mouth (25.22%), and headache (24.18%). On carbamazepine, tremor (24.18%) was the most common side effect followed by drowsiness (22.74%) and constipation (15.24%). One patient was dropped due to development of rash. On sodium valproate, tremor (14.42%) was the most common side effect followed by diarrhea/constipation (13.78%) and headache (8.36%) [Table 15].
Table 2: Comparison of clinical variables in the three treatment groups

| Clinical variables                                    | Treatment group | Mean±SD | df | F   | P    |
|-------------------------------------------------------|-----------------|---------|----|-----|------|
| Age (years)                                           | Lithium         | 15.33±1.72 | 2  | 0.28 | 0.756 |
|                                                       | Carbamazepine   | 15.40±1.50 |    |      |      |
|                                                       | Sodium valproate| 15.70±1.75 |    |      |      |
| Total number of past manic episode                    | Lithium         | 0.16±0.46   | 2  | 1.71 | 0.188 |
|                                                       | Carbamazepine   | 0.30±0.732   |   |      |      |
|                                                       | Sodium valproate| 0.52±0.79    |   |      |      |
| Past number of depressive episodes                     | Lithium         | 0.26±0.44    | 2  | 0.71 | 0.491 |
|                                                       | Carbamazepine   | 0.20±0.41    |    |      |      |
|                                                       | Sodium valproate| 0.11±0.33    |    |      |      |
| Duration of index episode (days)                       | Lithium         | 48.93±54.45  | 2  | 0.44 | 0.643 |
|                                                       | Carbamazepine   | 34.90±36.19  |    |      |      |
|                                                       | Sodium valproate| 48.11±70.90  |    |      |      |
| Total number of episodes (including index episode)     | Lithium         | 1.43±0.67    | 2  | 0.59 | 0.556 |
|                                                       | Carbamazepine   | 1.40±0.75    |    |      |      |
|                                                       | Sodium valproate| 1.64±0.86    |    |      |      |

df – Degree of freedom; P<0.05; F – ANOVA value. SD – Standard deviation

Table 3: Comparison of the clinical variables of the lithium, carbamazepine, and sodium valproate groups

| Variables                           | Lithium group | Carbamazine group | Sodium valproate group |
|-------------------------------------|---------------|-------------------|------------------------|
|                                     | n            | χ² (df), P        | n         | χ² (df), P        | n         | χ² (df), P        |
| Sex                                 |              |                   |            |                   |            |                   |
| Male                                | 16           | 2.71 (1), 0.100   | 14         | 2.14 (1), 0.143   | 13        | 1.12 (1), 0.290   |
| Female                              | 14           | 6                 | 4          |                   |            |                   |
| Family history                      |              |                   |            |                   |            |                   |
| Nil                                 | 14           | 6.73 (2), 0.034   | 13         | 2.05 (2), 0.359   | 10        | 3.66 (2), 0.160   |
| Affective                           | 15           | 4                 | 6          |                   |            |                   |
| Nonaffective                        | 1            | 3                 | 1          |                   |            |                   |
| Number of past manic episode        |              |                   |            |                   |            |                   |
| Nil                                 | 26           | 1.36 (2), 0.507   | 16         | 2.14 (2), 0.343   | 11        | 4.53 (2), 0.103   |
| One                                 | 3            | 3                 | 3          |                   |            |                   |
| Two                                 | 1            | 1                 | 3          |                   |            |                   |
| Past number of depressive episodes   |              |                   |            |                   |            |                   |
| One                                 | 22           | 1.09 (2), 0.295   | 16         | 0.95 (2), 0.329   | 15        | 7.36 (2), 0.007   |
| Two                                 | 8            | 4                 | 2          |                   |            |                   |
| Type of onset of index episode       |              |                   |            |                   |            |                   |
| Abrupt                              | 9            | 2.40 (2), 0.300   | 8          | 2.84 (2), 0.241   | 12        | 0.04 (2), 0.825   |
| Acute                               | 17           | 11                | 5          |                   |            |                   |
| Insidious                           | 4            | 1                 | 0          |                   |            |                   |
| Total number of episodes (including index episode) |          |                   |            |                   |            |                   |
| One                                 | 20           | 0.54 (2), 0.761   | 14         | 0.68 (2), 0.712   | 10        | 7.72 (2), 0.021   |
| Two                                 | 7            | 5                 | 3          |                   |            |                   |
| Three                               | 3            | 0                 | 4          |                   |            |                   |
| Four                                | 0            | 1                 | 0          |                   |            |                   |

df – Degree of freedom; χ² – Chi-square value; P<0.05

DISCUSSION

The sample size of our study group consists of 67 patients (30 patients were allotted to lithium group, 20 patients to carbamazepine group, and 17 patients to the sodium valproate group). Though the sample size was modest, it is larger than previous studies done on mood stabilizers in child and adolescent population. It has been a truism in child psychiatry that “Comorbidities are a rule rather than exception.” In contrast to this statement, the sample size of this study consisted of only patients with BD I which is considered to be statistically sound as compared to previous studies, which included various comorbidities such as ADHD and substance abuse.
Table 4: Comparison of Cassidy Scale for Manic States scores across the three treatment groups

| CSMS       | Treatment group        | Mean±SD       | df | F   | P     |
|------------|------------------------|---------------|----|-----|-------|
| Baseline   | Lithium                | 45.03±7.26    | 2  | 1.814 | 0.171 |
|            | Carbamazepine          | 44.00±8.22    |    |      |       |
|            | Sodium valproate       | 48.47±6.746   |    |      |       |
| First week | Lithium                | 24.00±8.97    | 2  | 0.045 | 0.956 |
|            | Carbamazepine          | 25.65±9.24    |    |      |       |
|            | Sodium valproate       | 24.82±12.99   |    |      |       |
| Second week| Lithium                | 17.20±7.89    | 2  | 1.347 | 0.267 |
|            | Carbamazepine          | 22.00±12.98   |    |      |       |
|            | Sodium valproate       | 16.94±13.66   |    |      |       |
| Third week | Lithium                | 15.97±11.11   | 2  | 0.684 | 0.508 |
|            | Carbamazepine          | 20.35±11.90   |    |      |       |
|            | Sodium valproate       | 16.52±15.44   |    |      |       |
| Fourth week| Lithium                | 17.36±12.28   | 2  | 1.941 | 0.152 |
|            | Carbamazepine          | 21.70±11.04   |    |      |       |
|            | Sodium valproate       | 16.52±15.44   |    |      |       |
| Fifth week | Lithium                | 13.30±11.45   | 2  | 1.492 | 0.233 |
|            | Carbamazepine          | 18.95±15.36   |    |      |       |
|            | Sodium valproate       | 12.00±14.52   |    |      |       |

df – Degree of freedom; P<0.05; F – ANOVA value; CSMS – Cassidy Scale for Manic States; SD – Standard deviation

Table 5: Comparison of reduction in Cassidy Scale for Manic States scores across the three treatment groups

| CSMS                  | Treatment group        | Mean±SD       | df | F   | P     |
|-----------------------|------------------------|---------------|----|-----|-------|
| Reduction in CSMS up to the 1st week | Lithium                | 20.52±9.19    | 2  | 1.58 | 0.213 |
|                        | Carbamazepine          | 20.20±7.11    |    |      |       |
|                        | Sodium valproate       | 20.52±9.19    |    |      |       |
| Reduction in CSMS up to the 2nd week | Lithium                | 27.02±11.92   | 2  | 3.26 | 0.045 |
|                        | Carbamazepine          | 25.82±9.09    |    |      |       |
|                        | Sodium valproate       | 22.00±11.99   |    |      |       |
| Reduction in CSMS up to the 3rd week | Lithium                | 28.11±13.33   | 2  | 1.95 | 0.150 |
|                        | Carbamazepine          | 29.06±11.21   |    |      |       |
|                        | Sodium valproate       | 25.82±15.02   |    |      |       |
| Reduction in CSMS up to the 4th week | Lithium                | 28.08±14.10   | 2  | 4.51 | 0.014 |
|                        | Carbamazepine          | 27.66±12.70   |    |      |       |
|                        | Sodium valproate       | 22.30±14.00   |    |      |       |
| Reduction in CSMS up to the 5th week | Lithium                | 31.73±12.68   | 2  | 3.31 | 0.043 |
|                        | Carbamazepine          | 25.05±14.51   |    |      |       |
|                        | Sodium valproate       | 36.47±14.20   |    |      |       |

CSMS – Cassidy scale for manic states; SD – Standard deviation; df – Degree of freedom; P<0.05; F – ANOVA value

The three groups in this study, i.e. lithium (n = 30), carbamazepine (n = 20), and sodium valproate (n = 17) included more patients, than previous studies comparing these three mood stabilizers. Previous studies had not assessed patients on a weekly basis, which is an improvement in methodology. Assessment of patients on a weekly basis could identify minor change in the psychopathology throughout the treatment trial as fluctuations in the psychopathology are very common in the child and adolescent psychiatry. Regarding dose and serum level, dose was adjusted only after getting the serum level on a weekly basis, which gives almost timely attainment of an adequate serum level. This is an improvement over a previous study which assessed serum level at only 2, 4, and 6 weeks. No other study till now has titrated the dose on the basis of serum level on a weekly basis.

Comparing the patients at the time of entry and the patients at completion of the study shows that this study has less dropouts than that of previous studies. In this study, out of 67 patients, 37 (55.22%) completed the 6-week study protocol as compared to three (7.14%) out of 42 patients completed an 8-week study.

In this study, the tool used for diagnosis was K-SADS-PL version, which is at par with earlier studies, and it is
considered a good diagnostic tool as it assesses the current condition as well the lifetime diagnosis.[29]

For assessing psychopathology, CSMS was used which could assess mixed features which is typical of pediatric mania. Most of the previous studies had used Young Mania Rating Scale (YMRS), which assesses more of euphoric mania symptoms.[29-31,34] In this study, UKU side effect checklist was used along with the side effect checklist of lithium, carbamazepine, and sodium valproate. Due to this, side effects related to antipsychotic and mood stabilizers could be assessed separately, which strengthens the study. Most of the earlier studies done on this area used only the side effect checklist of mood stabilizers.[29] Regarding concurrent medications used along mood stabilizer trial, we used only typical antipsychotic (CPZ or haloperidol). Atypical antipsychotics were not used as it is said to have mood stabilizing properties.[30] Earlier studies used stimulants, clonazepam, and clonidine, etc., along with the mood stabilizer trial.[31]

**Table 6: Dose of mood stabilizer (mg/day) across the three treatment groups**

| Dose of mood stabilizer (mg/day) | Treatment group | Mean±SD |
|---------------------------------|----------------|---------|
| **Dose of mood stabilizer at baseline** | Lithium | 890.00±38.05 |
| | Carbamazepine | 400.00±16.00 |
| | Sodium valproate | 882.35±159.04 |
| **Dose of mood stabilizer at the 1st week** | Lithium | 1075.00±131.14 |
| | Carbamazepine | 555.00±82.55 |
| | Sodium valproate | 976.47±139.32 |
| **Dose of mood stabilizer at the 2nd week** | Lithium | 1165.00±140.28 |
| | Carbamazepine | 650.00±119.20 |
| | Sodium valproate | 1105.88±198.33 |
| **Dose of mood stabilizer at the 3rd week** | Lithium | 1120.00±161.13 |
| | Carbamazepine | 680.00±136.11 |
| | Sodium valproate | 1129.41±208.46 |
| **Dose of mood stabilizer at the 4th week** | Lithium | 1250.00±186.15 |
| | Carbamazepine | 710.00±165.11 |
| | Sodium valproate | 1141.74±193.83 |
| **Dose of mood stabilizer at the 5th week** | Lithium | 1250.00±186.15 |
| | Carbamazepine | 680.00±164.16 |
| | Sodium valproate | 1141.74±193.83 |

SD – Standard deviation

**Table 7: Comparison of Udvalg for Kliniske Undersogelser-total score week wise across the three treatment groups**

| UKU rating score | Treatment group | Mean±SD | df | F | P |
|------------------|----------------|---------|----|---|---|
| **First week** | Lithium | 11.23±5.57 | 2 | 0.34 | 0.708 |
| | Carbamazepine | 11.20±5.33 | | | |
| | Sodium valproate | 10.17±3.30 | | | |
| **Second week** | Lithium | 8.37±3.94 | 2 | 1.98 | 0.146 |
| | Carbamazepine | 7.20±3.18 | | | |
| | Sodium valproate | 6.05±2.97 | | | |
| **Third week** | Lithium | 6.00±3.57 | 2 | 1.28 | 0.285 |
| | Carbamazepine | 6.50±4.92 | | | |
| | Sodium valproate | 4.52±2.83 | | | |
| **Fourth week** | Lithium | 5.20±4.05 | 2 | 1.35 | 0.265 |
| | Carbamazepine | 4.85±2.65 | | | |
| | Sodium valproate | 3.64±1.41 | | | |
| **Fifth week** | Lithium | 3.83±3.35 | 2 | 0.45 | 0.639 |
| | Carbamazepine | 4.05±2.18 | | | |
| | Sodium valproate | 3.23±1.67 | | | |

UKU – Udvalg for Kliniske Undersogelser Side Effect Rating Scale; df – Degree of freedom; F < 0.05; F – ANOVA value; SD – Standard deviation

Demographic variables

The sample of this study was predominantly male (64.20%) compared to females (35.80%).

The mean age of the patients in our study was 15.33 ± 1.72 years in lithium group, 15.40 ± 1.50 years in the carbamazepine group, and 15.70 ± 1.75 years in the sodium valproate group. In an earlier study,[29] the mean age was 11.40 years across the lithium, carbamazepine, and the sodium valproate groups. In two other studies,[30,31] the mean age was 12.1 ± 3.62 years and 12.3 ± 3.7 years respectively. The mean age in our study is more than the mean age of patients in earlier studies. This disparity can be due to the characteristic of the Indian society. In our society, females and very young children only infrequently opt for inpatient management due to cultural reasons and fear of being stigmatized. Majority of the study sample were Hindu (80.60%) compared to Muslims (19.40%). This finding could be due to the predominant Hindu population in the catchment area of this tertiary care hospital.

Comparison of the mood stabilizers

In this study, the mean duration of the index episode was 48.93 ± 54.45 days in the lithium group, 34.90 ± 36.19 days...
in the carbamazepine group, and 48.11 ± 70.90 days in the sodium valproate group. This result shows the typical pattern of childhood BD, which is known for its chronicity and long episodes.\[50\] Chi-square test was done to show the association of clinical variables across the lithium, carbamazepine, and sodium valproate groups. The result showed a significant association of use of lithium with the presence of a family history of BD. There is also a significant association of use of sodium valproate with the number of past depressive episodes and total number of episodes. This result supports earlier finding of the research done on predictors of mood stabilizer response.\[37\] This can be of important bearing in the selection of mood stabilizer for a particular case. It can be seen from the result that there is an abrupt fall of an average of 20.52 ± 9.19 points in the lithium group, 20.20 ± 7.11 points in the carbamazepine group, and 18.35 ± 6.82 points in the sodium valproate group in the CSMS at the 1st week. This finding can be explained by the use of high dose of antipsychotic in initial few days to control aggression. This finding is in agreement with the results of an earlier study, which showed similar reduction on CSMS at the end of the 1st week.\[29\] The result also shows the time required across the treatment group for getting therapeutic level of each mood stabilizer. The time required for therapeutic level is in the 2nd week for the lithium group, 1st week in carbamazepine group, and 3rd week in case of sodium valproate. The “therapeutic serum level” is defined as 0.8–1.2 mmol per liter for lithium, 8–12 µg per liter for carbamazepine, and 85–110 µg per liter for sodium valproate. This result is comparable with that of an earlier study.\[29\] The reason for attainment of adequate serum level in the 3rd week in case of the sodium valproate group is the use of a very narrow range (85–110 µg per liter) as defining therapeutic range in our study.

The results of our study show a gradual decline in the UKU-side effect rating scale, but the requirement of trihexyphenidyl remains almost same across the three treatment groups throughout the study period. This can be explained by high rates of dystonia in the three groups. The occurrence of dystonia requires the need of prophylactic trihexyphenidyl in the risk-prone group of child population.\[38\]
Singh, et al.: Effect size of lithium, carbamazepine, and sodium valproate

Table 10: Post hoc test showing requirement of mean antipsychotic (chlorpromazine equivalent) dose and Cassidy Scale for Manic States change from baseline to end of the study using multiple comparison across the three treatment groups

| Dependent variable                        | Multiple comparison | Treatment group | Treatment group | Mean difference | P     | 95% CI          |
|-------------------------------------------|---------------------|-----------------|-----------------|----------------|-------|-----------------|
| Mean antipsychotic (CPZ equivalent)       | Lithium             | Carbamazepine   | −87.50          | 0.014          | −156.37 | −18.62         |
|                                           |                     | Sodium valproate| −75.41          | 0.042          | −147.84 | −2.99          |
|                                           | Carbamazepine       | Lithium         | 87.50           | 0.014          | 18.62   | 156.37         |
|                                           |                     | Sodium valproate| 12.08           | 0.760          | −66.61  | 90.78          |
|                                           | Sodium valproate    | Lithium         | 75.41           | 0.042          | 2.99    | 147.84         |
|                                           |                     | Carbamazepine   | −12.08          | 0.760          | −90.78  | 66.61          |
| CSMS change from baseline to end of the study | Lithium             | Carbamazepine   | 12.52           | 0.337          | −4.11   | 29.16          |
|                                           |                     | Sodium valproate| −5.80           | 0.510          | −23.30  | 11.69          |
|                                           | Carbamazepine       | Lithium         | −12.52          | 0.337          | −29.16  | 4.11           |
|                                           |                     | Sodium valproate| −18.32          | 0.059          | −37.34  | 0.68           |
|                                           | Sodium valproate    | Lithium         | 5.80            | 0.510          | −11.69  | 23.30          |
|                                           |                     | Carbamazepine   | 18.32           | 0.059          | −0.68   | 37.34          |

P<0.05. CI – Confidence interval; CPZ – Chlorpromazine; CSMS – Cassidy Scale for Manic States

Table 11: Comparison of serum level week wise across the three treatment groups

| Serum level | Treatment group | Mean±SD |
|-------------|-----------------|---------|
| First week  | Lithium         | 0.58±0.23 |
|             | Carbamazepine   | 9.53±4.34 |
|             | Sodium valproate| 49.21±18.21 |
| Second week | Lithium         | 0.84±0.26 |
|             | Carbamazepine   | 10.94±2.54 |
|             | Sodium valproate| 59.21±21.70 |
| Third week  | Lithium         | 0.90±0.26 |
|             | Carbamazepine   | 10.69±3.00 |
|             | Sodium valproate| 90.99±29.66 |
| Fourth week | Lithium         | 0.88±0.23 |
|             | Carbamazepine   | 10.90±3.36 |
|             | Sodium valproate| 101.22±17.93 |
| Fifth week  | Lithium         | 1.08±1.10 |
|             | Carbamazepine   | 10.60±2.29 |
|             | Sodium valproate| 124.41±54.34 |

SD – Standard deviation

The result of post hoc test using LSD model of requirement of mean antipsychotic (CPZ equivalent) dose and CSMS score for manic state change from baseline to end of the study using repeated-measures ANOVA shows the comparison across the three treatment groups using CSMS and CSMS versus lithium carbonate, carbamazepine, and sodium valproate. First, the effect of change of CSMS over the 6 weeks across the three treatment group was determined, which was found to be highly statistically significant (at 0.000 level). Then, the effect of the change of CSMS was compared with lithium carbonate, carbamazepine, and sodium valproate. All the three groups were compared using repeated-measures ANOVA. The results were not found to be statistically

In this study, we also calculated the response rate of lithium, carbamazepine, and sodium valproate on the basis of ≥33% reduction from baseline and CSMS and CGI-BP improvement Score of 1 or 2. We got a response rate of 70% in lithium group, 65% in carbamazepine group, and 82% in sodium valproate group on the basis of ≥50% reduction from baseline YMRS and CGI-BP improvement Score of 1 or 2. Previous study by Kowatch et al. showed a response rate of 46%–50% for divalproex sodium, 42%–45% for lithium, and 34%–44% for carbamazepine on the basis of ≥50% reduction from baseline YMRS and CGI-BP improvement Score of 1 or 2. The discrepancy regarding response rate can be explained by the fact that our study used a cutoff of 33% reduction rather than 50%, along with use of antipsychotic in the initial week to control aggression.

The result of multivariate tests using repeated-measures ANOVA shows the comparison across the three treatment groups using CSMS and CSMS versus lithium carbonate, carbamazepine, and sodium valproate. First, the effect of change of CSMS over the 6 weeks across the three treatment group was determined, which was found to be highly statistically significant (at 0.000 level). Then, the effect of the change of CSMS was compared with lithium carbonate, carbamazepine, and sodium valproate. All the three groups were compared using repeated-measures ANOVA. The results were not found to be statistically
Table 12: Multivariate tests showing comparison across the three treatment groups using Cassidy Scale for Manic States and Cassidy Scale for Manic States versus lithium carbonate, carbamazepine, and sodium valproate groups using repeated-measures ANOVA

| Variables                                                | Effect Value | df | F    | P      | Partial η² |
|----------------------------------------------------------|--------------|----|------|--------|------------|
| CSMS                                                     | Wilks' Lambda | 0.115 | 5.00 | 92.15  | 0.000      | 0.885      |
| CSMS versus lithium carbonate, carbamazepine, and sodium valproate groups | Wilks' Lambda | 0.826 | 10.00 | 1.20   | 0.296      | 0.091      |

df – Degree of freedom; P<0.05. F – ANOVA value. CSMS – Cassidy Scale for Manic States

Table 13: Intent-to-treat sample: Percentage of responders in each treatment group by response variable

| Drug                     | Response variables | n/all (%) | Mean of CGI-BP and CSMS response (%) |
|--------------------------|--------------------|-----------|--------------------------------------|
|                          |                    |           | CGI-BP change score of 1 or 2      | ≥33% reduction in baseline CSMS |
| Lithium carbonate        |                   | 21/30 (70)| 27/30 (90)                          | 80                           |
| Carbamazepine            |                   | 13/20 (65)| 14/20 (70)                          | 67                           |
| Sodium valproate         |                   | 14/17 (82)| 15/17 (88)                          | 85                           |

CGI-BP – Clinical Global Impression-Bipolar Version; CSMS – Cassidy Scale for Manic States

As regards the tolerability of these three mood stabilizers in pediatric mania, our results show a side effect profile of the patients on lithium carbonate, in which tremor (38.76%) was the most common side effect followed by thirst (28.90%), dry mouth (25.22), and headache (24.18%). The side effect profile of the patients on carbamazepine showed tremor (24.18%) as the most common side effect followed by drowsiness (22.74%) and constipation (15.24%).

Only one out of twenty patients developed rashes in the 2nd week for which carbamazepine was stopped. The side effect profile of the patients on sodium valproate was tremor (14.42%) followed by diarrhea/constipation (13.78%) and headache (8.36%). Our results show the tolerability of these agents in treating BD in children, which supports earlier studies done in this group.[29-31] To summarize, the finding of this study is comparable to that of the earlier studies. It can be said that the cumulative time for response data suggests that adequate trial in childhood BD should be at least 6–8 weeks, but this finding can only be generalized after studying a large group of pediatric population for a long duration of time.

**Limitations**

The sample size in this study was modest and their distribution across the treatment groups was uneven. Antipsychotics were used to control aggression and the follow-up period was limited.

**CONCLUSIONS**

Adolescent Bipolar 1 disorder patients during Manic phase showed an ES of 0.85 for lithium, 0.71 for carbamazepine, and 0.84 for sodium valproate. These agents are well tolerated in treating BD in children.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.
Table 15: Side effect profile of patients on lithium carbonate, carbamazepine, and sodium valproate

| Lithium (n=30) | Percentage | Carbamazepine (n=20) | Percentage | Sodium valproate (n=17) | Percentage |
|----------------|------------|----------------------|------------|-------------------------|------------|
| Tremor         | 38.76      | Tremor               | 24.18      | Tremor                  | 14.42      |
| Headache       | 24.38      | Headache             | 14.94      | Headache                | 8.36       |
| Anorexia       | 10.46      | Decreased appetite   | 6.88       | Decreased appetite/heart burn | 7.76       |
| Nausea         | 6.56       | Nausea               | 5.98       | Nausea                  | 6.88       |
| Vomiting       | 1.20       | Vomiting             | 0.30       | Vomiting                | 0.30       |
| Diarrhea       | 1.80       | Diarrhea             | 1.20       | Diarrhea/constipation    | 13.78      |
| Stomach pain   | 6.90       | Stomach pains        | 4.78       | Bloated abdomen          | 7.48       |
| Dry mouth      | 25.22      | Dry mouth            | 14.04      |                         |            |
| Urinary frequency | 11.06 | Drowsiness            | 22.74      | Drowsiness               | 6.58       |
| Thirst         | 28.90      | Feeling dizzy        | 5.98       | Dizziness                | 4.48       |
| Blurry vision  | 0.30       | Blurred vision       | 2.00       | Tingling of hands/feet   | 0.30       |
| Fatigue        | 24.48      | Double vision        | 0.90       | Muscle weakness          | 3.58       |
| Metallic taste | 3.00       | Constipation         | 15.24      | Weight gain              | 4.20       |
| Feeling hot/cold| 0.90      | Unsteady gait        | 0.90       | Unsteady gait            | 0.30       |
| Weight gain    | 5.30       | Muscle ache          | 0.90       |                         |            |
| Confusion      | 3.90       | Tinnitus             | 0.30       |                         |            |
| Acne           | 2.40       | Skin rash            | 1.20       |                         |            |
| Itchiness      | 0.30       |                      |            |                         |            |
| Folliculitis   | 0.90       |                      |            |                         |            |
| Seborrhea      | 0.30       |                      |            |                         |            |

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