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Addenbrooke's Cognitive Examination-III Performance in Euthymic Bipolar Disorder During Maintenance Treatment With Lithium Versus Sodium Valproate: A Cross-Sectional Comparative Study.

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Abstract

Background: Cognitive impairment may persist during euthymia in bipolar disorder and can limit functional recovery. Evidence directly comparing global and domain-specific cognitive performance during lithium and sodium valproate maintenance treatment remains limited. ***Methods:*** This hospital-based cross-sectional comparative study included 100 adults aged 18-50 years with DSM-5 bipolar disorder who had remained euthymic for at least 2 months and had received lithium (n=51) or sodium valproate (n=49) for at least 6 months. Euthymia was defined as Young Mania Rating Scale score <=7 and Hamilton Depression Rating Scale score <=8. Cognition was assessed exclusively with the Addenbrooke's Cognitive Examination-III (ACE-III). The prespecified principal outcome was ACE-III total score; attention/orientation, memory, verbal fluency, language, and visuospatial scores were secondary outcomes. Welch independent-samples t tests, mean differences with 95% confidence intervals, Hedges g, and Holm-adjusted p values for the five domain comparisons were reported. ***Results:*** The lithium group had a higher ACE-III total score than the sodium valproate group (73.29 +/- 8.68 vs 67.57 +/- 9.37; mean difference 5.72, 95% CI 2.13-9.31; t(96.7)=3.16; p=0.021). Unadjusted differences favored lithium for attention/orientation (p=0.0497), memory (p=0.0231), and verbal fluency (p=0.0465), whereas language (p=0.279) and visuospatial performance (p=0.301) did not differ significantly. ***Conclusions:*** In this tertiary-care sample, sodium valproate treatment was associated with lower ACE-III total and verbal-fluency performance than lithium treatment. The cross-sectional, non-randomized design does not establish a causal medication effect, and residual confounding by illness characteristics and concomitant treatment remains possible.

Keywords: Addenbrooke's Cognitive Examination-III; bipolar disorder; cognition; euthymia; lithium; sodium valproate; verbal fluency.

INTRODUCTION

Bipolar disorder is a recurrent psychiatric illness characterized by episodes of mania or hypomania and depression. It is associated with substantial disability, impaired occupational and social functioning, suicide risk, and a frequent need for long-term maintenance treatment [1-4]. Symptomatic remission is an important treatment goal, but the absence of a current mood episode does not necessarily imply restoration of cognitive or functional health.

Cognitive dysfunction is increasingly recognized as a clinically important dimension of bipolar disorder. Systematic reviews and meta-analyses have identified persistent deficits during euthymia across attention, processing speed, verbal learning and memory, working memory, and executive functioning [5-9]. The degree of impairment is heterogeneous: some patients perform close to normative expectations, whereas others experience clinically meaningful difficulties that may interfere with treatment adherence, employment, independent living, and psychosocial recovery [5-9].

The cognitive contribution of maintenance medication is difficult to distinguish from the effects of the disorder itself. Lithium remains a core treatment for relapse prevention and suicide-risk reduction, while sodium valproate is widely used for mania and maintenance treatment [3,4]. A meta-analysis suggested that lithium may exert small adverse effects on selected cognitive functions, particularly immediate verbal learning and memory [10]. However, subsequent observational and longitudinal studies have not demonstrated a uniform global disadvantage and have sometimes observed stable or improved performance during successful lithium treatment [14,15].

Comparative studies of lithium and valproate have also produced mixed results. In the STOP-EM study, valproate-treated patients showed poorer working-memory performance, whereas most other tested domains did not differ between treatment groups [11]. Another study reported impaired immediate verbal memory in both lithium- and valproate-treated euthymic patients without broad between-group differences [12]. Comparative computerized testing has nevertheless suggested that valproate may be associated with greater impairment across selected domains in some clinical samples [13]. Differences in illness stage, previous episode burden, residual symptoms, education, serum drug concentration, and concomitant psychotropic exposure may account for part of this inconsistency.

The Addenbrooke's Cognitive Examination-III (ACE-III) provides a standardized 100-point assessment of global cognition and five component domains: attention/orientation, memory, verbal fluency, language, and visuospatial ability [18]. The present study used ACE-III to compare global and domain-specific cognitive performance in euthymic adults with bipolar disorder receiving maintenance treatment with lithium or sodium valproate. The principal hypothesis was that ACE-III total score would differ between the two treatment groups; domain analyses were treated as secondary comparisons.

AIMS

To study the Cognitive Dysfunction in persons with Bipolar Affective Disorder receiving Sodium Valproate and Lithium at Tertiary Care Hospital.

Objectives of the Study

- To study the cognitive impairment in persons with bipolar disorders who are on Lithium and Sodium valproate.
- To compare both groups (Lithium and Sodium valproate) for cognitive impairment.

MATERIALS AND METHODS

Study design, setting, and reporting

A hospital-based cross-sectional comparative study was conducted over 12 months in the Department of Psychiatry of a tertiary-care teaching hospital in Government General Hospital, Sangareddy, Telangana, India. Participants were recruited by convenience sampling from outpatient services. Reporting was aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19].

Participants and diagnostic procedure

Adults aged 18-50 years were eligible if they met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for bipolar disorder [2], had remained in clinical remission for at least 2 months, and had received either lithium or sodium valproate as a mood stabilizer for at least 6 months. Diagnosis was established by psychiatric clinical assessment using DSM-5 criteria. Current manic symptoms were rated using the Young Mania Rating Scale (YMRS) [16], and depressive symptoms were rated using the Hamilton Depression Rating Scale (HAM-D) [17]. Euthymia was operationally defined as YMRS <=7 and HAM-D <=8. Participants were required to have adequate vision and hearing and to provide written informed consent. Exclusion criteria were another current mental disorder, including substance dependence; diagnosed diabetes mellitus or hypertension; neurological comorbidity; and learning difficulty. The final sample comprised 100 participants: 51 receiving lithium and 49 receiving sodium valproate.

Assessment instruments and outcomes

Table 1. Diagnostic and cognitive assessment instruments

Instrument	Construct	Administration and scoring	Role in study
DSM-5 clinical criteria	Diagnostic classification	Bipolar disorder diagnosis established through psychiatric assessment using DSM-5 criteria [2]	Eligibility and diagnostic classification
YMRS	Current manic symptoms	Eleven clinician-rated items; higher scores indicate greater manic symptom severity [16]	Euthymia threshold <=7
HAM-D	Current depressive symptoms	Clinician-rated depressive symptom severity; higher scores indicate greater depressive symptom burden [17]	Euthymia threshold <=8
ACE-III	Global and domain-specific cognition	Attention/orientation 18 points, memory 26, verbal fluency 14, language 26, visuospatial ability 16; total 100; higher scores indicate better performance [18]	Principal outcome: total score; secondary outcomes: five component scores

ACE-III, Addenbrooke's Cognitive Examination-III; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HAM-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

Sociodemographic and clinical characteristics were collected with a standardized proforma and included age, sex, education, marital status, socioeconomic status, occupation, illness duration, and treatment duration. The ACE-III total was calculated as the sum of its five component scores. The total score was defined as the principal cognitive outcome because it provides an overall estimate of cognitive performance; the five component scores were analyzed as secondary outcomes.

Data validation and statistical analysis

The original dissertation database was analyzed in IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Participant-level ACE-III data were independently reanalyzed for this manuscript using Python 3.13.5, NumPy 2.3.5, and SciPy 1.17.0. Medication coding was verified as 0=lithium and 1=sodium valproate. All 100 participants had complete ACE-III total and component data; no imputation was performed. Continuous variables are presented as mean and standard deviation. Categorical variables are presented as number and percentage. Welch independent-samples t tests were used for continuous between-group comparisons because they do not require equal population variances. For each ACE-III outcome, the lithium-minus-valproate mean difference, 95% confidence interval (CI), Welch t statistic with Satterthwaite degrees of freedom, exact two-sided p value, and Hedges g were calculated. Positive mean differences and positive Hedges g values indicate higher performance in the lithium group. The ACE-III total was the principal outcome. To control family-wise error across the five secondary component comparisons, Holm-adjusted p values were calculated. Statistical significance was defined as two-sided $p<0.05$. Mann-Whitney U tests were used as nonparametric sensitivity analyses for the principal and domain outcomes.

Ethics

Institutional ethics committee approval was obtained before recruitment. Participants received information about the study and provided written informed consent. Participation was voluntary, and withdrawal did not affect clinical care. The institutional approval identifier was not present in the supplied dissertation record and should be inserted from the ethics documentation before submission.

RESULTS

Participant characteristics

All 100 enrolled participants were included in the analysis. Fifty-one participants were receiving lithium and 49 were receiving sodium valproate. Mean age, sex distribution, education, socioeconomic status, occupation, illness duration, and treatment duration did not differ significantly between groups. Marital status differed between groups (p=0.033), with a greater proportion of married participants in the lithium group.

Table 2. Sociodemographic and clinical characteristics by treatment group

Characteristic	Lithium (n=51)	Sodium valproate (n=49)	Test statistic	p value
Age, years	32.67 +/- 9.37	33.59 +/- 9.06	Welch t=-0.50; df=98.0	0.619
Duration of illness, years	5.10 +/- 2.58	5.40 +/- 2.84	Welch t=-0.55; df=96.2	0.582
Duration of treatment, years	5.10 +/- 2.93	5.27 +/- 2.78	Welch t=-0.30; df=98.0	0.767
Age group, n (%)	18-25: 15 (29.4); 26-35: 14 (27.5); 36-45: 18 (35.3); 46-50: 4 (7.8)	18-25: 12 (24.5); 26-35: 17 (34.7); 36-45: 16 (32.7); 46-50: 4 (8.2)	Chi-square=0.70; df=3	0.873
Sex, n (%)	Male: 27 (52.9); Female: 24 (47.1)	Male: 25 (51.0); Female: 24 (49.0)	Fisher exact test	1.000
Education, n (%)	None: 13 (25.5); Primary: 10 (19.6); Secondary: 9 (17.6); Higher: 19 (37.3)	None: 15 (30.6); Primary: 12 (24.5); Secondary: 9 (18.4); Higher: 13 (26.5)	Chi-square=1.41; df=3	0.703
Marital status, n (%)	Single: 9 (17.6); Married: 35 (68.6); Separated: 7 (13.7)	Single: 17 (34.7); Married: 21 (42.9); Separated: 11 (22.4)	Chi-square=6.81; df=2	0.033

Socioeconomic status, n (%)	Lower: 25 (49.0); Middle: 9 (17.6); Upper: 17 (33.3)	Lower: 18 (36.7); Middle: 16 (32.7); Upper: 15 (30.6)	Chi-square=3.19; df=2	0.203
Occupation, n (%)	Clerk: 8 (15.7); Labourer: 18 (35.3); Manager: 9 (17.6); Professional: 6 (11.8); Unemployed: 10 (19.6)	Clerk: 5 (10.2); Labourer: 9 (18.4); Manager: 10 (20.4); Professional: 16 (32.7); Unemployed: 9 (18.4)	Chi-square=8.31; df=4	0.081

Values are mean +/- SD or n (%). All tests are unadjusted and two-sided.

ACE-III total and component outcomes

The lithium group had a higher ACE-III total score than the sodium valproate group (mean difference 5.72 points, 95% CI 2.13-9.31; p=0.021), corresponding to a moderate standardized difference (Hedges g=0.63). At the component level, unadjusted comparisons favored lithium for attention/orientation, memory, and verbal fluency. Language and visuospatial scores did not differ significantly.

After Holm correction across the five component analyses, verbal fluency remained statistically significant (adjusted p=0.028), whereas attention/orientation (adjusted p=0.149) and memory (adjusted p=0.093) did not. Nonparametric sensitivity tests supported the direction of the principal total-score and verbal-fluency findings

Table 3. ACE-III total and component outcomes by treatment group

Outcome	Lithium mean +/- SD	Valproate mean +/- SD	Li-VPA difference (95% CI)	Welch t (df)	Unadjusted p	Holm-adjusted p	Hedges g
ACE-III total	73.29 +/- 8.68	67.57 +/- 9.37	5.72 (2.13 to 9.31)	3.16 (96.7)	0.021	Not applicable: principal outcome	0.63
Attention/orientation	12.47 +/- 3.16	11.04 +/- 3.96	1.43 (0.002 to 2.86)	1.99 (91.8)	0.0497	0.149	0.40
Memory	19.22 +/- 3.31	17.88 +/- 2.43	1.34 (0.19 to 2.49)	2.31 (91.7)	0.0231	0.093	0.46
Verbal fluency	11.16 +/- 2.16	9.55 +/- 2.34	1.61 (0.71 to 2.50)	3.57 (96.6)	0.0465	0.028	0.71
Language	19.45 +/- 3.29	18.76 +/- 3.11	0.70 (-0.57 to 1.96)	1.09 (98.0)	0.279	0.558	0.22
Visuospatial	11.00 +/- 2.80	10.35 +/- 3.43	0.65 (-0.59 to 1.90)	1.04 (92.7)	0.301	0.558	0.21

ACE-III, Addenbrooke's Cognitive Examination-III; CI, confidence interval; Li-VPA, lithium minus sodium valproate. Higher scores indicate better performance. Positive differences and positive Hedges g values favor lithium. Holm correction was applied to the five component outcomes only.

DISCUSSION

This study compared ACE-III performance in euthymic adults with bipolar disorder receiving maintenance treatment with lithium or sodium valproate. The principal finding was a 5.72-point higher mean ACE-III total score in the lithium group, with a 95% confidence interval excluding zero and a moderate standardized effect. Among the five ACE-III components, verbal fluency showed the clearest separation and remained significant after correction for multiple domain comparisons. Attention/orientation and memory differed in unadjusted analyses but did not remain significant after Holm correction, while language and visuospatial performance were similar between groups.

The finding of lower global cognitive performance in the sodium valproate group is compatible with evidence that cognitive functioning in euthymic bipolar disorder is heterogeneous and can be influenced by both illness characteristics and treatment exposure [5-9]. The recent domain-specific meta-analysis found moderate impairment across several cognitive domains in euthymic bipolar disorder, while also emphasizing substantial unexplained variability between studies and

individuals [5]. Accordingly, the observed between-group difference should be interpreted within a broader model that includes premorbid ability, education, episode burden, residual symptoms, comorbidity, and medication exposure.

The verbal-fluency result is clinically and neuropsychologically plausible. ACE-III fluency tasks require lexical retrieval, initiation, sustained search, speeded production, and executive organization. A lower score may therefore reflect inefficiency across several processes rather than a pure language deficit. This interpretation is supported by the absence of a significant difference in the broader ACE-III language component. The moderate-to-large fluency effect also remained statistically significant after family-wise error correction, making it the most robust component-level finding in the present dataset.

Previous direct comparisons of lithium and valproate have not produced a uniform pattern. The STOP-EM study identified poorer working-memory performance with valproate but did not find broad differences across all domains [11]. Senturk and colleagues reported immediate verbal-memory impairment in both treatment groups without generalized between-group cognitive separation [12]. Gualtieri and Johnson observed differences across several computerized cognitive measures among patients receiving different mood stabilizers, with valproate among the less favorable profiles [13]. These studies differ from the present work in illness stage, cognitive battery, treatment history, sample size, and control of confounding.

Lithium should not be interpreted as uniformly cognition-enhancing. The meta-analysis by Wingo and colleagues found small adverse effects on selected cognitive outcomes [10]. Conversely, Burdick and colleagues found no baseline generalized disadvantage among lithium users and observed improvement in several measures after mood stabilization with lithium monotherapy [14]. Longitudinal work has also shown that cognitive deficits may persist despite successful lithium treatment and remain associated with psychosocial functioning [15]. The current results therefore indicate a treatment-group association, not proof that lithium improves cognition or that valproate directly causes impairment.

Confounding by indication is an important alternative explanation. Sodium valproate may be selected for patients with a different polarity profile, episode pattern, behavioral activation, rapid cycling, previous treatment response, or tolerability history. Cognitive performance may also be influenced by antipsychotics, benzodiazepines, anticholinergic burden, sleep disturbance, thyroid dysfunction, serum drug concentrations, and medication adherence. These factors were not sufficiently documented for adjusted participant-level analysis. The marital-status imbalance observed between groups further illustrates that treatment groups were not formed by random allocation.

Clinically, the findings support asking about cognitive and functional difficulties during maintenance treatment rather than assuming that euthymia represents complete recovery. ACE-III can provide a structured overview of global and component performance, but it is a screening instrument and does not replace a comprehensive neuropsychological assessment. When clinically meaningful cognitive difficulty is identified, potentially reversible factors should be reviewed before attributing impairment to a single mood stabilizer or changing an otherwise effective treatment.

Future research should use prospective designs with pretreatment cognitive assessment, repeated ACE-III or comprehensive neuropsychological measurement, documented medication doses and serum levels, and systematic recording of concomitant psychotropic exposure. Multivariable regression, propensity-score methods, or randomized allocation would help separate treatment effects from confounding by indication. Replication across multiple centers and linguistic groups would also improve generalizability.

Strengths

- The study provides a direct comparison of two widely used maintenance mood stabilizers in a clinically relevant euthymic sample.
- Participant-level ACE-III data were available for all 100 participants, allowing exact reanalysis of the total and five component scores.
- The principal outcome was separated from secondary component analyses, and multiplicity was addressed with Holm correction.

Limitations

- The cross-sectional design prevents determination of temporal sequence or causality, and pretreatment cognitive performance was unavailable.
- Treatment assignment was non-random, and adjusted analyses could not account for education in years, episode burden, psychosis history, residual symptoms, medication dose, serum concentration, adherence, thyroid status, sleep, or concomitant psychotropic exposure.

- Convenience sampling from one tertiary-care center and restriction to adults aged 18-50 years limit generalizability.
- The absence of a healthy control group prevents estimation of impairment relative to population norms.
- ACE-III is a cognitive screening instrument and does not provide the depth of a comprehensive neuropsychological battery.
- The study also included patients who were on antipsychotics along with Sodium valproate and Lithium which might have impacted the cognition and metabolic parameters.

Future directions

- Conduct longitudinal studies to track cognitive and metabolic changes over time in patients treated with Lithium and Sodium valproate.
- Implement multi-center studies to enhance the generalizability of findings and provide a comprehensive understanding across diverse populations.
- Include control groups of patients not on mood stabilizers or on different medications to establish a baseline for comparison.
- Investigate the underlying biological mechanisms that lead to cognitive impairments and metabolic changes in patients on mood stabilizers.
- Explore the effects of combination therapies, such as using cognitive enhancers or metabolic interventions alongside mood stabilizers, to improve patient outcomes.

CONCLUSION

In this hospital-based cross-sectional sample of euthymic adults with bipolar disorder, participants receiving sodium valproate had lower ACE-III total and verbal-fluency scores than participants receiving lithium. Attention/orientation and memory differences were less robust after correction for multiple comparisons, and language and visuospatial scores were similar. These findings should be interpreted as associations and require prospective replication with baseline cognition, treatment-dose data, serum concentrations, and adjustment for clinical and medication-related confounding.

Declarations

Ethics approval and consent to participate: Institutional ethics committee approval was obtained before recruitment, and all participants provided written informed consent. The approval identifier should be inserted from the institutional record before submission.

Consent for publication: Not applicable; no individual participant is identifiable in this report.

Availability of data and materials: De-identified participant-level data are held by the investigator and institution and may be considered for sharing on reasonable request, subject to ethics and institutional approval.

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Competing interests: The author declares no competing interests.

Author contribution: S.K. conceptualized the study with academic supervision, recruited participants, collected and curated data, interpreted the findings, and drafted the manuscript.

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