ADJUNCTIVE ANTIDEPRESSANT THERAPY FOR ACUTE BIPOLAR I DEPRESSION: A MULTI-CENTER OPEN LABEL TRIAL

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INTRODUCTION:

- Depressive symptoms and episodes are 3 times more common than mania[1] and are associated significant burden to the patient and the family[2].
- There is limited and conflicting data on the efficacy of antidepressants for treatment of bipolar I depression[3].
- Despite this, clinicians use antidepressants widely in clinical practice settings[4].
- However, the clinical trials with antidepressants are sparse.

OBJECTIVES:

- To assess the efficacy and safety of adjunctive antidepressants (escitalopram/bupropion XL) in the treatment of acute bipolar I depression over 16 weeks.

METHODOLOGY:

- Adults (≥18 years) with DSM –V diagnosis of acute bipolar I depression (MADRS score ≥ 20) ≥ 2 weeks but ≤ 52 weeks who were on therapeutic doses of mood stabilizers (lithium or divalproex) or a second-generation antipsychotic (SGA) (risperidone, olanzapine, quetiapine, aripiprazole or ziprasidone) or their combination were recruited from Canada, Korea, and India from 2009 to 2020.
- We chose escitalopram 10-30 mg/day and bupropion XL 100-450mg/day as the antidepressants for the study as they are the most widely used antidepressants for treating bipolar depression.
- Patients were commenced on adjunctive therapy with one of these antidepressants and the trial lasted for upto 16 weeks. The dose of the medications was titrated based on response and tolerability.
- Patients were assessed every 2 weeks or more frequently depending on clinical need until 16 weeks.
- The primary outcome was remission (MADRS scores ≤ 8) from depression. The other outcomes included response and switch to mania/hypomania.
- Institutional Ethics Committee approval was obtained before the commencement of the study.
- Data analysis was done using SPSS version 28.0

RESULTS:

- 209 patients were recruited and 14 patients lost to follow-up, 18 patients withdrew consent , 2 patients were not adherent to medications, 4 were excluded based on psychiatrist's opinion and unknown reasons.
- A total of 197 patients were included in the analysis (missing data = 12).
- The socio-demographic details and clinical details of these patients are tabulated in table 1 and 2 respectively.

Primary outcome:

- Change in the MADRS scores from baseline to end-point was statistically significant, as shown by the Wilcoxan signed rank test p = 0.00 (Baseline = 26.5 ± 4.79, Endpoint = 5.0 ± 5.92)

Secondary outcomes:

- The rates of remission (MADRS ≤ 8, YMRS ≤ 8 and response (>50% reduction in the MADRS score) is 84.6% (169/197) and 78.2% (154/197) respectively.
- The rates of mania (YMRS ≥ 20) and hypomania (YMRS ≥ 16) were 3.5% and 1.5% respectively.
- There were no serious adverse events in the trial.
- The median time to remission was 6 weeks.
- Figure 1 and 2 illustrate the survival analysis of time to remission and response respectively.

TABLE 1: SOCIO-DEMOGRAPHIC DETAILS

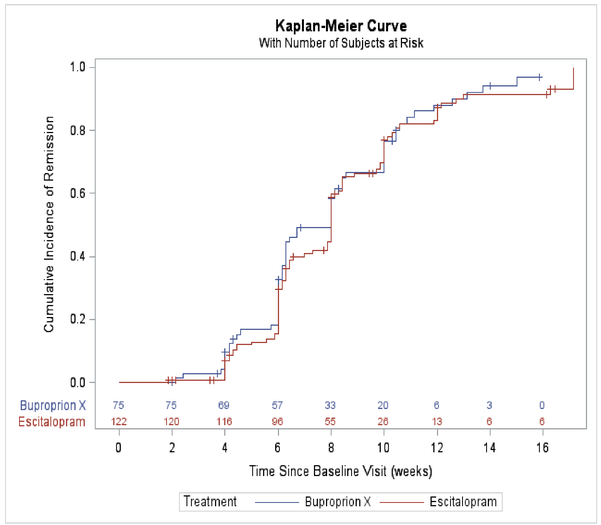
SOCIO-DEMOGRAPHIC DETAILS	MEAN ± SD/FREQUENCY(%) N = 197
Age	40.28 ± 11.27 (Median - 40) years
Sex	
Male	94 (47.7)
Female	103 (52.3)
Race	
Asian	172(87.3)
Black	1(0.5)
Caucasian	23(11.7)
Other	1(0.5)
Marital status	
Single	48(24.4)
Married	131(66.5)
Divorced	7(3.5)
Widowed	8(4.1)
Common-Law partner	3(1.5)

TABLE 2: CLINICAL VARIABLES

CLINICAL VARIABLES	MEAN ± SD/FREQUENCY(%) N = 197
Location of treatment	
Inpatient	5(2.5)
Outpatient	192(97.5)
Number of Previous mood episodes	
Mania	2.86 ± 8.1
Depression	2.86 ± 8.13
Hypomania	1.61 ± 10.39
Mixed	1.14 ± 10.0
Duration of current episode in months	2.61 ± 2.65 (minimum 2 weeks, maximum 86 weeks)
Duration of illness in years	12.64 ± 9.23
Age at onset of illness in years	27.87 ± 8.7
DRUG COMBINATION	
Bupropion XL + Mood stabilizer	32(16.2)
Bupropion XL + Mood stabilizer +SGA	34(17.3)
Bupropion XL + SGA	9(4.6)
Escitalopram + Mood stabilizer	52(26.4)
Escitalopram + Mood stabilizer + SGA	59(29.9)
Escitalopram + SGA	11(5.6)

Survival analysis of time to remission

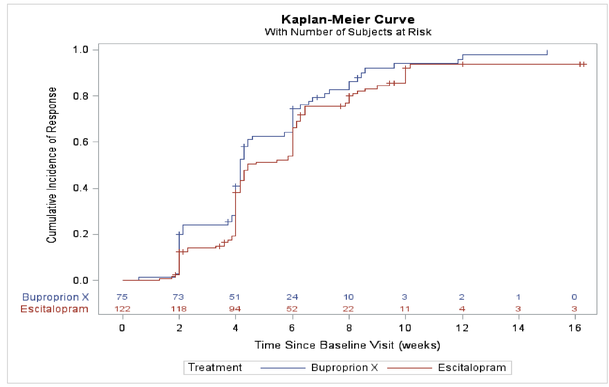
FIGURE 1: Kaplan-Meier Curve for time to remission



- Kaplan-Meier estimated remission at week 16 was 0.94 for Bupropion X and 0.91 for Escitalopram

Survival analysis of time to response

FIGURE 2: Kaplan-Meier curve for Response



- Kaplan-Meier estimated response at week 16 was 1 for Bupropion XL and 0.94 for Escitalopram.

CONCLUSION:

- Adjunctive antidepressant therapy with escitalopram/ bupropion is effective and safe in the treatment of bipolar I depression.
- In combination with the therapeutic doses of mood stabilizers/Second generation antipsychotics, there is lesser risk of mania/hypomania.

REFERENCE / BIBLIOGRAPHY:

1. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59(6):530–7.
2. Calabrese JR, Hirschfeld RMA, Frye MA, Reed ML. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. J Clin Psychiatry 2004;65(11):1499–504.
3. Yatham LN, Kennedy SH, Parikh S V, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20(2):97–170.
4. Reddy YJ, Jhanwar V, Nagpal R, et al. Prescribing practices of Indian psychiatrists in the treatment of bipolar disorder. Aust N Z J Psychiatry 2019;53(5):458–69.

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