

Levetiracetam in the Management of Bipolar Depression: A Randomized, Double-blind, Placebo Controlled Trial

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OBJECTIVE

- Levetiracetam is a novel antiepileptic drug that shows evidence of possibly unique activity in the hippocampus and the amygdala that have been widely implicated in bipolar disorder.
- Levetiracetam has been shown to have an antidepressant profile in an animal model.
- In an open label add-on trial with levetiracetam, treatment resistant bipolar disorder patients with depressive symptoms showed a 31% remission rate.
- This study investigated the efficacy of adjunctive levetiracetam therapy compared with placebo in subjects with bipolar depression.
- **The primary hypothesis:** Patients treated with levetiracetam would have a greater change in Hamilton Depression Rating Scale (HDRS, 21-item) score from baseline to endpoint than patients treated with placebo.

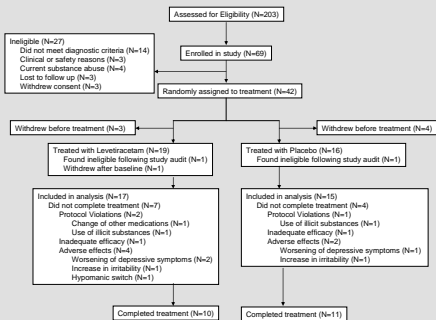


Figure 1: CONSORT diagram

METHODS

- Placebo controlled, double-blind trial
- Randomly assigned 42 outpatients with Bipolar Disorder Type 1 and Type 2.
- All patients were experiencing a major depressive episode (HDRS > 17).
- Patients received treatment either with placebo or adjunctive levetiracetam (up to 2500 mg/day flexibly dosed) for 6 weeks (see Figure 1).
- The primary efficacy measure: Mean change from baseline to week 6 in the HDRS score.
- Secondary efficacy measures: Montgomery-Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Clinical Global Impression Scale for use in bipolar illness (CGI-BP), Hamilton Anxiety Rating Scale (HARS).

Patient Characteristics	Levetiracetam Group (N=17)		Placebo Group (N= 15)		Statistics		
	Mean	Std Dev	Mean	Std Dev	t(30)=	p=	
Age	46.2	11.1	41.2	8.5	1.41	0.17	
Age of onset for bipolar disorder	18.6	9.3	13.8	8.4	1.54	0.13	
Duration of bipolar disorder (yrs)	27.5	11.7	27.5	11.0	0.01	0.99	
Duration of current depressive episode (wks)	22.6	19.2	17.8	15.1	0.79	0.44	
Age of onset for first depressive episode	18.6	9.3	15.3	7.7	1.09	0.29	
Age of onset for first manic episode	25.1	10.7	22.6	13.0	0.58	0.57	
Number of failed medication trials	4.8	3.1	6.2	3.0	-1.28	0.21	
Number of psychiatric hospitalizations	3.5	7.1	2.8	2.6	0.38	0.71	
	N	%	N	%	X²(1)=	p=	
Gender, male	8	47.1	6	40.0	0.16	0.69	
Race							
	Caucasian	17	100.0	11	73.3	5.18	0.02
	Non-Caucasian	0	0.0	4	26.6		
Bipolar disorder type	I	12	70.6	11	73.3	0.03	0.86
	II	5	29.4	4	26.7		
History of suicide attempt(s)	5	29.4	7	50	1.37	0.24	
Number of depressive episodes	<20	4	23.5	2	13.3	0.54	0.46
	>=20	13	76.5	13	86.7		
Number of manic episodes	<20	6	35.3	4	26.7	0.28	0.6
	>=20	11	64.7	11	73.3		
Baseline Psychometric Assessments	Mean	SD	Mean	SD	t(30)=	p=	
HDRS score	23.2	5.6	18.2	6.7	0.45	0.66	
MADRS score	28.5	6.6	22.1	8.3	0.68	0.5	
HARS score	18.4	5.1	14.5	5.1	0.66	0.51	
YMRS score	4	2.3	4.3	2	1.01	0.32	
BDI score	28	11.5	22.1	8.5	1.58	0.12	
CGI-BP depression severity score	4.1	0.8	3.4	0.9	-0.57	0.57	

Table 1: Patient characteristics

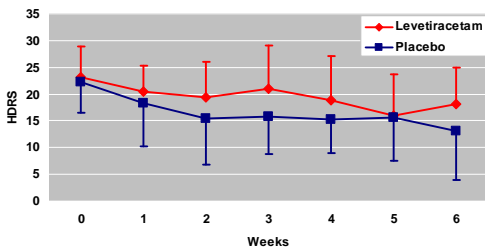


Figure 2: HDRS scores in depressed patients with bipolar disorder taking levetiracetam or placebo. Group by time interaction: $F(5,115)=1.25$, $p=0.29$.

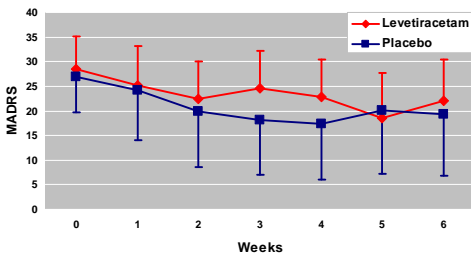


Figure 3: MADRS scores in depressed patients with bipolar disorder taking levetiracetam or placebo. Group by time interaction: $F(5,114)=2.09$, $p=0.07$.

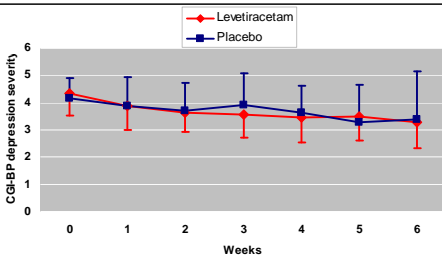


Figure 4: CGI-BP depression severity scores in depressed patients with bipolar disorder taking levetiracetam or placebo. Group by time interaction: $F(5,114)=0.47$, $p=0.79$.

RESULTS

- 42 subjects randomized to placebo or levetiracetam.
- 32 received at least one post baseline assessment and were available for analysis.
- No statistically significant differences between the groups for any of the demographic factors studied (Table 1).
- The baseline scores for HDRS, MADRS, HARS, YMRS, BDI and CGI-BP depression severity were comparable between the 2 groups (all p values > 0.12, see Table 1).
- The mean (SD) levetiracetam daily dose at endpoint evaluation was 1132(425) mg/day.
- All the statistics performed were based on the change from baseline.
- No statistically significant difference in the mean change from baseline to week 6 in the HDRS scores for levetiracetam compared with placebo (Fig 2).
- No statistically significant differences in any of the secondary outcome measures (all p > 0.05).

CONCLUSIONS

- In this randomized, double-blind, placebo-controlled study, levetiracetam adjunctive therapy did not show superior efficacy to placebo in the acute treatment of bipolar depression.
- It does not appear that the lack of separation from placebo was due to patient sampling bias or a high placebo response.

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