Levetiracetam as an Adjunctive Treatment for Mania: A Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract
Background: Levetiracetam is an anticonvulsant with a low side effect profile and favorable properties for individuals with bipolar I disorder during their manic phase. Despite initial promising results until about 2008, it appears that this track of research has not been followed-up. To counter this, we tested the influence of adjuvant levetiracetam on acute mania, compared to placebo. More specifically, we performed a randomized, double-blind, placebo-controlled clinical trial among inpatients with bipolar disorder I during their acute phase of mania. ***Methods:*** A total of 72 inpatients (mean age: 33.98 years; 23.6% females) with diagnosed bipolar disorder I and during their acute manic phase were randomly assigned either to the adjuvant levetiracetam (250 mg to a maximum of 1,500 mg) or to the placebo condition. Standard medication was lithium at therapeutic dosages. At baseline, participants completed a series of self-rating questionnaires covering sociodemographic information and subjective sleep. Subjective sleep was re-assessed 24 days later at the end of the study. Experts rated participants' acute state of mania with the Young Mania Rating Scale at baseline and at day 12 and day 24. Participants' cognitive performance was assessed at baseline and at day 24 at the end of the study. ***Results:*** Over time, mania scores significantly decreased (large effect size), but more so in the levetiracetam condition, compared to the placebo condition (medium effect size). Likewise, over time, subjective sleep improved (large effect size), but more so in the levetiracetam condition, compared to the placebo condition (large effect size). Over time, cognitive performance improved (large effect size), irrespective of the study condition. ***Conclusions:*** Compared to placebo, adjuvant levetiracetam to lithium improved symptoms of mania, as rated by experts, and subjective sleep quality. Adjuvant levetiracetam had no further favorable (or detrimental) impact on cognitive performance.

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Introduction

Typically, individuals with bipolar disorders suffer from recurrent and intense fluctuations of mood, energy, and behavior [1–3]. In the same vein, individuals with bipolar disorder describe that their mood swings are persistent, intense, frequent, and disrupting the continuity of private, educational, professional, social, cognitive, emotional, behavioral, and economic stability [1–5].

Next, bipolar disorders affect the economically most active population [1] and the population with the highest pressure to prevail and assert for successful mating [6–8], that is to say, the onset of mood fluctuations is often the psychosexually, psychosocially, and economically demanding developmental stage of early adulthood. Next, the average time lapse between disease onset and diagnose and first treatment is 5 to 10 years [1]; such a gap of time might be well explained because clinical observations suggest that bipolar disorders are often not recognized or under-diagnosed [1–3]. In this view, it is conceivable that the following prevalence rates might be underestimated: lifetime prevalence rates are 0.6% for bipolar disorder I, 0.4% for bipolar disorder II, 1.4% for subthreshold bipolar disorder II, and 2.4% for bipolar disorder spectrum [9].

To specify the diagnosis, both the ICD-10/11 [10, 11] and the DSM-5 [12] characterize bipolar disorders as a chronic psychiatric disease with the presence of manic (bipolar disorder I) or hypomanic (bipolar disorder II) episodes and major depressive disorders [13]. Next, compared to the general population, individuals with bipolar disorder have an increased risk of premature death, which might be a direct consequence of suicide; indeed, and compared to the general population, the risk of death by suicide is up to 20 times higher in individuals with bipolar disorders [1–3].

Besides excessive mood swings, individuals with bipolar disorder also show higher cognitive dysfunctions [2], both at short-term during the manic phase, and at long-term during the life span [14, 15]. Not surprising, and compared to the general population, individuals with bipolar disorder and during their acute phase of mania showed impaired cognitive flexibility [16] and impaired verbal and working memory performance [17]. Next, a severe course of illness was associated with higher impairments of cognitive performance [17], along with lower executive function and verbal memory, and it is irrespective of the acute manic/hypomanic or depressed stage [18]. Given these results, we investigated the change of cognitive performance during the beginning of the pharmacological treatment of a manic phase. More specifically, we investigated if levetiracetam adjuvant to lithium could have improved the cognitive impairment, compared to placebo.

Next, compared to the general and healthy population, individuals with bipolar disorder report more impaired sleep [10–12], and the associations between higher illness intensity and illness oscillations and irregular sleep patterns have gained more attention [1–3]. Importantly, individuals in a manic state and at the beginning of the psychopharmacologic treatment are at increased risk to report severe sleep disruptions. Given this assumption, the second aim of the present study was to investigate to what extent adjuvant levetiracetam to the standard treatment with lithium could improve the subjective sleep quality, when compared to placebo.

As mentioned above, the acute phase of mania is particularly critical, and its pharmacologic treatment is particularly demanding. Mood stabilizers such as lithium, sodium valproate, carbamazepine, and lamotrigine, and the so-called second-generation antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone are administered (just to name but a few; see [2, 3] for a comprehensive overview). However, side effects appear to be the main reasons to quit from medication treatment [19]. Typical side effects of the so-called first-generation antipsychotics (e.g., chlorpromazine and haloperidol) were Parkinson's disease-like movements, internal restlessness, and tardive dyskinesia; typical side effects of the so-called second-generation antipsychotics are on metabolism, leading to weight gain, insulin-resistance [20–22], and extrapyramidal adverse effects [23].

In this regard, levetiracetam is an anticonvulsant with less side effects and favorable properties for manic stages. Initially, levetiracetam was developed as a nootropic (memory enhancing) drug, although levetiracetam turned out to be a potent anticonvulsant and marketed as a treatment for partial seizures [24]. Interestingly, between 2002 and 2011, there was some interest on the influence of levetiracetam on manic stages in individuals with bipolar disorder. Goldberg and Burdick [25] reported the case study of a person in a manic stage; levetiracetam monotherapy (500 mg–2,500 mg/d) was given for 5 consecutive weeks. At the third week, scores of the Young Mania Rating Scale (YMRS) decreased by 50%. Grunze et al. [26] performed the first open-label and add-on study. 10 individuals with bipolar disorder during their manic phase were treated with haloperidol and adjuvant levetiracetam (up to 4,000 mg/d); mean YMRS scores decreased

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from 29.2 to 14.7 after 2 weeks. Post et al. [27] performed the next un-blind and 8 weeks lasting interventional study with adjunctive levetiracetam (500 mg up to 2,000 mg/d) to standard mood stabilizers among 34 individuals with bipolar disorder during their manic phase and labeled as treatment-resistant. Adjuvant levetiracetam improved symptoms of mania. Clinically relevant improvements were observed in 16 out of 21 patients (76.2%) in manic stages, in 5 out of 13 patients (38.5%) in depressive states; in 4 out of 16 patients (25%) with cycling characteristics moderate to marked exacerbation was observed. Kyomen [28] reported 6 case studies of older individuals with mania (mean age: 69.6 years); the mean YMRS was 35.8 at baseline and 11.3 12 days after regular and daily levetiracetam administration. Desarkar et al. [29] analyzed the change of mania intensity of a 14-year-old female adolescent during her manic stage; treatment response was clearly observable when levetiracetam (750 mg) was added to the carbamazepine standard treatment. Krüger et al. [30] compared in a randomized clinical trial the effect of adjuvant levetiracetam (up to 5,000 mg/d) to valproate sodium versus valproate sodium monotherapy (up to 3,000 mg/d). Compared to sodium valproate, adjuvant levetiracetam did not improve symptoms of mania. Saricicek et al. [31] performed a double-blind placebo-controlled clinical trial to investigate the effect of adjuvant levetiracetam in patients with bipolar disorder during their phase of depression. It turned out that compared to placebo and 6 weeks after treatment, levetiracetam did not improve symptoms of depression, as both rated by patients and experts.

Overall, results from these case studies, open-label add-on studies, and one randomized clinical trial were such that levetiracetam appeared to be a promising medication to treat symptoms of mania, but not symptoms of depression in individuals with bipolar disorder. However, surprisingly, research interest on this topic appeared to have ceased. This is even more astonishing, when giving a closer look at the properties of levetiracetam. While the most common side effects of levetiracetam include drowsiness, dizziness, ataxia, diplopia, memory impairment, apathy, and paresthesia, there are few if any interactions with other drugs, including other anticonvulsants and above all with lithium (see [32] for more details). Overall, Boland et al. [32] concluded that the low laboratory interactions, the cognitive enhancing properties, and the low side effects should make levetiracetam a relatively new treatment option for mania.

To counter this gap or research, but above all to investigate new and additional possibilities to treat indi-viduals during their manic phase, and to alleviate their critical mental health state, we expanded upon previous findings in the following 6 ways. (1) The sample size was quite large ($N = 72$); (2) the study design was a double-blind, placebo-controlled clinical trial; (3) levetiracetam was given adjunctively to lithium, a standard mood stabilizer; (4) we relied on both participants' and experts' ratings; (5) we assessed not only the intensity of mania, as rated by experts, but also assessed participants' cognitive performance; (6) we assessed subjective sleep quality.

Given the controversial results as mentioned above, we did not formulate hypotheses, but three research questions. The first research question we asked was whether levetiracetam adjuvant to lithium improved symptoms of mania, compared to placebo. The second research question we asked was if levetiracetam adjuvant to lithium improved sleep disturbances, when compared to placebo. The third research question we asked was if levetiracetam adjuvant to lithium improved cognitive performances, when compared to placebo.

We hold that the present results might be of both clinical and practical importance, as the study results could improve the pharmacologic treatment of individuals in an acute manic state. This claim holds particularly true as regard to participants' cognitive performance and sleep quality. First, there is extant research to show that both cognitive performance [2, 14–17, 33, 34] and sleep [1–3] are deteriorated during the manic state; second, to our knowledge, the effect of levetiracetam on cognitive performance and sleep was not investigated so far.

Methods

Procedure
Inpatients of the Sina Hospital of Hamadan (Hamadan, Iran) with diagnosed bipolar disorder and currently in an acute phase of mania were approached to participate in this double-blind study. Participants were fully informed about the study design and about the confidential and secure data handling. Further, they were informed that participation or non-participation had no advantages or disadvantages for the current treatment regimen and treatment quality. Participants signed the written informed consent. Thereafter, they were assigned either to the adjuvant levetiracetam or to the (adjuvant) placebo condition. Participants completed the Pittsburgh Sleep Quality Index (PSQI) at baseline and at day 24, at the end of the study. Experts blind to participants' study condition assignment rated participants' intensity of mania with the YMRS (see below) at baseline, day 12, and day 24, the end of the study. Participants' cognitive performance was rated with the Mini Mental State Examination (MMSE) at baseline and at day 24. The study was registered at the Iran Clinical Trial Register (IRCT20120215009014N295). The local Ethics Committee ap-

proved the study (IR.UMSHA.REC.1398.352), which was performed in accordance with the seventh and current edition [35] of the Declaration of Helsinki. The primary outcome was the change in symptoms of mania and secondary outcomes were subjective sleep disturbances and cognitive performance.

Sample Size Calculation

The sample size calculation was performed with G*Power® [36]. As mentioned above, studies on the effect of (adjuvant) levetiracetam on acute mania were performed about 15 years ago. For want of reliable data, the sample size calculation assumed to achieve at least a medium effect size ($\eta_p^2 > 0.059$); given this, the following sample size was calculated: $\eta_p^2 > 0.059$; $f = 0.253$; alpha = 0.05; power (1-beta error probability) = 0.99, groups = 2; measurements = 3; epsilon correction = 0.9; total sample size: 64; to compensate for possible dropouts, the sample size was set at $N = 84$.

Randomization

As in other studies [37–40], randomization was accomplished with randomization.com to create a list to assign 84 participants randomly to 1 of the 2 study conditions. Based on this list, a psychologist not otherwise involved in the study prepared 84 sealed envelopes with either a blue (= levetiracetam) or a red (= placebo) card, and put them in an opaque ballot box. Once a participant has drawn the envelope, the psychologist assigned the participant to the specific group, and the envelope was destroyed, that is, not put in the ballot box again.

Measurements
Demographic and Treatment-Related Information
Participants reported their age (years), gender (male, female), civil status (single, married), employment status (employed, unemployed), educational level (diploma or lower, academic degree) and further, tobacco use (yes, no).

### Severity of Mania, YMRS, and Expert Ratings
Experts assessed participants' mania severity with the Farsi version [41] of YMRS [42]. The YMRS consists of 11 items; 7 items are graded from 0 to 4, and 4 items are graded from 0 to 8. The total score ranges from 0 to 60, with a higher score reflecting a higher severity of mania.

Subjective Sleep: Pittsburgh Sleep Index
To rate subjective sleep quality, participants completed the Farsi version [43–45] of the PSQI [46]. The PSQI is a self-report scale completed in 5 min. It consists of 19 items and contains 7 subscales (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleeping medication, and daytime dysfunction), each weighted equally on a scale from 0 to 3, with higher scores indicating poorer sleep quality. The 7 components are then summed to obtain an overall PSQI score, ranging from 0 (good sleep quality) to 21 (poor sleep quality). Total scores of ≥5 reflect poor sleep, associated with considerable sleep complaints (Cronbach's alpha = 0.85).

Cognitive Performance
To assess participants' cognitive performance, the Persian version [47, 48] of the MMSE [49] was employed. The MMSE has satisfactory psychometric properties [47, 48, 50]. This expert rating assessed participants' orientation to time and place, attention
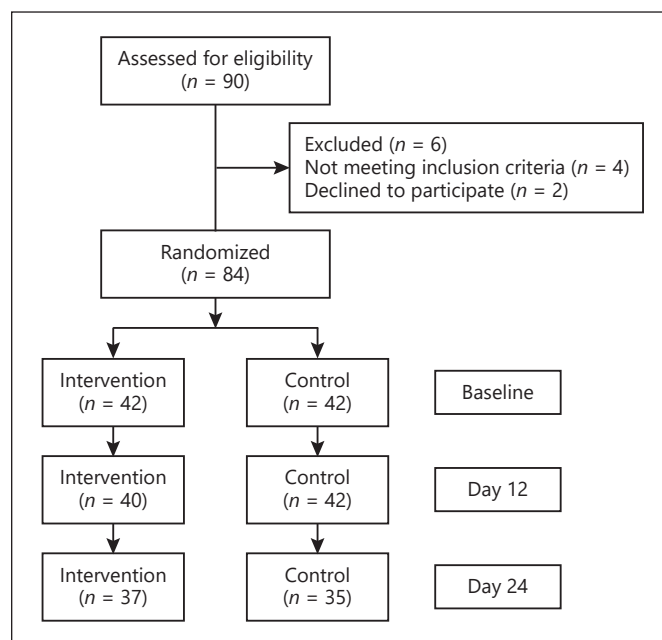
Fig. 1. Study overview, group allocation, and samples.

and calculation, recall, language, repetition and complex commands such as drawing shapes, with higher scores reflecting a higher cognitive performance; 24–30 points reflect normal cognitive performances, while scores of 23 and lower reflect an impaired cognitive performance.

Standard Medication
All patients received 900–1,200 mg/d of lithium carbonate tablet at 3 divided doses, such to achieve the therapeutic blood level of lithium (0.5–1.5 mmol/lit).

Levetiracetam
Participants in the levetiracetam condition received (pills of 500 mg/d to a maximum of 1,500 mg/day) of adjuvant levetiracetam in the morning and in the evening at 2 divided doses. Tolerance to levetiracetam was assessed daily. To this end, participants reported on a checklist (answers; yes vs. no), if one or more of the following side effects occurred; dizziness, sleepiness, dry mouth, ataxia, diplopia, memory impairment, apathy, and paresthesia.

Placebo
Participants in the placebo condition received placebo pills, which consisted of lactose powder, glycerin, methylparaben, and propylparaben. Pills of levetiracetam and placebo were identical in shape, color, weight, and smell. To keep the assessment identical to the levetiracetam assessment, tolerance to the placebo was assessed daily, and blood pressure was measured before and 1 h after placebo administration.

Statistical Analyses
Statistical analyses were performed as per the protocol. With a series of χ^2 tests and t tests, sociodemographic and illness-related information were compared between participants in the leveti-

Table 1. Descriptive and inferential statistical overview of sociodemographic and treatment-related information between participants in the levetiracetam condition and placebo condition

Variable	Groups		Statistics
	levetiracetam condition (N = 37)	placebo condition (N = 35)	
Age, mean (SD), years	33.49 (8.07)	34.51 (8.71)	$t(70) = 0.52$, $d = 0.17$ [T]
Episodes, n, mean (SD)	3.11 (2.58)	3.00 (2.09)	$t(70) = 0.16$, $d = 0.06$ [T]
Gender, n (%)			
Male	27 (37.5)	28 (38.9)	χ^2 (N = 72, df = 1) = 0.49
Female	10 (13.9)	7 (9.7)	
Civil status, n (%)			
Married	15 (20.8)	18 (16.0)	χ^2 (N = 72, df = 1) = 0.86
Single	22 (30.6)	17 (23.6)	
Employment status, n (%)			
Employed	10 (13.9)	6 (8.3)	χ^2 (N = 72, df = 1) = 1.02
Unemployed	27 (51.4)	29 (40.3)	
Education, n (%)			
Diploma or lower	18 (25)	21 (29.2)	χ^2 (N = 72, df = 1) = 0.93
Academic	19 (26.4)	14 (19.4)	
Tobacco use, n (%)			
Yes	25 (34.7)	27 (37.5)	χ^2 (N = 72, df = 1) = 0.82
No	12 (16.7)	8 (11.1)	
History of psychiatric disease, n (%)			
Yes	17 (23.6)	20 (27.8)	χ^2 (N = 72, df = 1) = 0.90
No	10 (27.8)	15 (20.8)	

[T], trivial effect size. All $p > 0.30$.

racetam and placebo condition. An ANOVA for repeated measures was performed with the following factors: time (baseline, day 12, and day 24), group (levetiracetam vs. placebo), and the time × group interaction; dependent variables were the YMRS scores. A series of ANOVAs for repeated measures was performed with the following factors: time (baseline; day 24), group (levetiracetam vs. placebo), and the time × group interaction; the dependent variables were the sleep disturbances and cognitive performance. A series of Pearson's correlations was performed between mania scores, cognitive performance and sleep quality at baseline, day 12 and day 24, separately for participants in the levetiracetam condition and placebo condition.

To compare the mean changes between and within the levetiracetam and the placebo condition, we followed Becker [51] and reported Cohen's *d*'s effect sizes, with the following cutoff values: $d < 0.19$ = trivial effect size; $0.20 < d < 0.49$ = small effect size; $0.50 < d < 0.79$ = medium effect size; $d > 0.80$ = large effect size [52]. Effect sizes for F-statistics were reported as partial eta squared (η_p^2), with $\eta_p^2 < 0.019$ = trivial effect size [T]; $0.020 < \eta_p^2 < 0.059$ = small effect size [S], $0.06 < \eta_p^2 < 0.139$ = medium effect size [M], and $\eta_p^2 \geq 0.14$ = large effect size [L]. The nominal significance level was set at alpha <0.05. All calculations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

Results

Participants

Figure 1 provides the flow chart of the number of participants approached, screened, and included in the study. Inclusion criteria were as follows: (1) age between 18 and 65 years; (2) diagnosis of bipolar disorder, based on the DSM-5 [12], and as ascertained by an experienced clinical psychologist or psychiatrist following a thorough clinical interview for DSM-5 disorders [53]; (3) YMRS: 20 or more points; (4) hospitalized for bipolar disorders for at least once within the last 2 years; (5) compliance with the study requirements; (6) signed written informed consent. Exclusion criteria were as follows: (1) known allergies against lithium, based on participants' self-reports and on medical records; (2) suicide attempt within the last 8 weeks before study admission; (3) risk of suicide attempts; (4) severe further psychiatric disorders such as substance use disorder, personality disorder, post-traumatic stress disorder, or adjustment disorder; (5) current use of additional anticonvulsants and antipsychotics, based on self-reports and medical records; (6) females: breastfeed-

Table 2. Descriptive statistical indices of severity of mania (YMRS), sleep quality (PSQI), and cognitive performance (MMSE) at baseline, day 12, and day 24 (end of the study), separately for participants in the levetiracetam and placebo condition

	Time points					
	baseline		day 12		day 24	
	levetiracetam	placebo	levetiracetam	placebo	levetiracetam	placebo
N	37	35	37	35	37	35
Mania severity (YMRS), mean (SD)	31.22 (5.86)	30.20 (4.33)	16.35 (6.31)	18.00 (4.32)	9.43 (3.79)	13.63 (5.59)
Sleep quality (PSQI), mean (SD)	9.62 (1.62)	9.14 (1.65)	–	–	4.16 (1.54)	6.09 (2.43)
Cognitive performance (MMSE), mean (SD)	23.86 (4.06)	22.60 (4.52)	–	–	26.05 (1.86)	25.37 (1.80)

YMRS, Young Mania Rating Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini Mental Status Examination.

Table 3. Inferential statistical indices of severity of mania (YMRS), sleep quality (PSQI) and cognitive performance (MMSE) over time and between and within the study conditions (levetiracetam vs. placebo)

	Factors			
	time	group	time × group interaction	Greenhouse-Geisser epsilon
Mania severity (YMRS)	$F_{(2, 140)}$ η_p^2 336.35*** 0.828 [L]	$F_{(1, 70)}$ η_p^2 3.75 0.051 [S]	$F_{(2, 140)}$ η_p^2 5.88** 0.078 [M]	0.789
Sleep quality (PSQI)	$F_{(1, 70)}$ η_p^2 217.91*** 0.757 [L]	$F_{(1, 70)}$ η_p^2 4.99* 0.067 [M]	$F_{(1, 70)}$ η_p^2 17.34*** 0.199 [L]	1
Cognitive performance (MMSE)	41.43*** 0.372 [L]	2.89 0.040 [S]	0.57 0.008 [T]	1

YMRS, Young Mania Rating Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini Mental Status Examination; [S], small effect size; [M], medium effect size; [L], large effect size; [T], trivial effect size. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

ing, pregnant, or planning to get pregnant the next 10 weeks.

As shown in Figure 1, of the 90 inpatients approached, 84 (93.3%) of them were included in the study and randomized, and 72 completed the study. Statistical calculations were performed per protocol.

General Information

Table 1 provides the descriptive and statistical overview of sociodemographic and treatment-related information between participants in the levetiracetam and placebo condition. Overall, participants in the levetiracetam and placebo condition did not differ as regards age, the number of episodes (trivial to small effect sizes), sociodemographic information, and medication treatment.

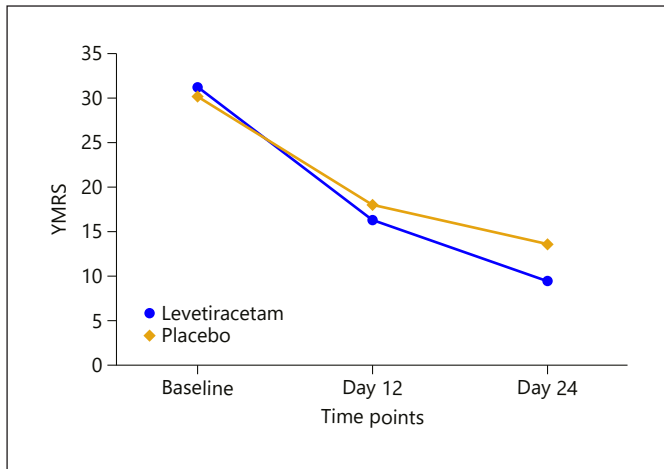YMRS Scores between and within the Levetiracetam and Placebo Group and over Time

Table 2 provides the descriptive statistical overview of the YMRS scores at baseline, day 12, and day 24 within and between the levetiracetam and placebo condition.

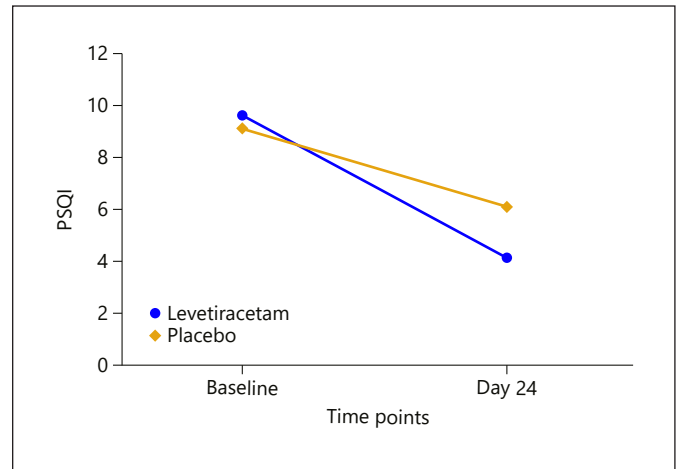Table 3 provides the inferential statistical overview (see also Fig. 2).

YMRS scores statistically significantly decreased from baseline to day 24 (large effect size), but more so in the levetiracetam condition, compared to the placebo condition (interaction with medium effect size). There was no group difference (small effect size).

Sleep Quality between and within the Levetiracetam and Placebo Group and over Time

Table 2 also provides the descriptive overview of sleep quality between and within the clonidine and placebo condition at baseline and day 24; Table 3 provides the inferential statistical overview (see also Fig. 3). Sleep quality statistically significantly improved over time (large effect size), but more so in the levetiracetam condition, compared to the placebo condition (interaction: medium effect size). Participants in the levetiracetam condition reported lower sleep disturbances, compared to the placebo condition (medium effect size).

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Fig. 2. Symptoms of mania over time and between and within the adjuvant levetiracetam and placebo condition. YMRS, Young Mania Rating Scale.

Fig. 3. Sleep disturbances over time and between and within the adjuvant levetiracetam and placebo condition. PSQI, Pittsburgh Sleep Quality Index.
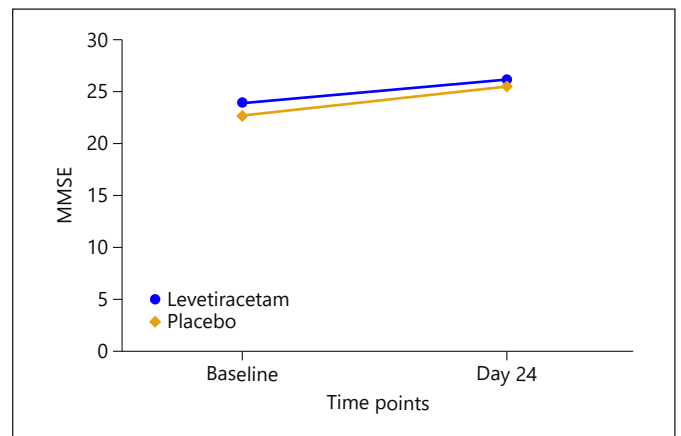
Cognitive Performance between and within the Levetiracetam and Placebo Group and over Time

Table 2 also provides the descriptive overview of cognitive performance between and within the levetiracetam and placebo condition at baseline and day 24; Table 3 provides the inferential statistical overview (see also Fig. 4). Cognitive performance statistically significantly improved over time (large effect size), although with no difference within and between the levetiracetam and placebo condition (trivial and small effect sizes).

Mean Changes between the Levetiracetam and Placebo Condition at the End of the Study (Day 24), and within the Levetiracetam and Placebo Condition from Baseline to the End of the Study

Table 4 provides the overview of effect size calculations (Cohen's *d*) between the levetiracetam and placebo condition at the end of the study, and within the levetiracetam and placebo condition from baseline to the end of the study. At the end of the study, mania scores and sleep disturbances (large effect sizes) were lower in the levetiracetam condition, compared to the placebo condition. No difference was observed for the cognitive performance (small effect size).

Within the levetiracetam condition, mania, sleep disturbances scores, and cognitive performance improved from baseline to the study end (large effect sizes). Within the placebo condition, mania, sleep disturbances scores, and cognitive performance improved from baseline to the study end (always large effect sizes).

Fig. 4. Cognitive performance over time and between and within the adjuvant levetiracetam and placebo condition. MMSE, Mini Mental Status Examination.

Correlations between Mania, Cognitive Performance, and Sleep Quality at Baseline, Day 12 and Day 24 (End of the Study), Separately for the Clonidine and Placebo Condition

Table 5 provides the overview of the correlations.

Levetiracetam Condition

At baseline, mania scores were unrelated to cognition and sleep at every time point. Cognitive performance predicted a higher cognitive performance at day 24, but also higher sleep disturbances. Otherwise, no further statisti-

Table 4. Overview of effect sizes; between-group comparisons at the end of the study; within-group comparisons from baseline to the end of the study

	Effect size comparisons		
	between the levetiracetam and placebo condition at the end of the study	within the levetiracetam condition from baseline to the study end	within the placebo condition from baseline to the study end
Mania severity (YMRS)	1.00 [L]	7.30 [L]	3.98 [L]
Sleep quality (PSQI)	0.88 [L]	3.20 [L]	1.41 [L]
Cognitive performance (MMSE)	0.38 [S]	1.17 [L]	1.55 [L]

YMRS, Young Mania Rating Scale; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini Mental Status Examination; [S], small effect size; [L], large effect size.

Table 5. Correlations between symptoms of mania, cognitive performance, and sleep at baseline, day 12 and day 24 (end of the study), separately for participants in the adjuvant levetiracetam condition or placebo condition

					Time points			
		Baseline			day 12	day 24		
		mania	cognition	sleep	mania	mania	cognition	sleep
Levetiracetam (N = 37)								
Baseline	Mania	–	0.02	0.12	0.24	0.12	0.07	0.04
	Cognition	0.02	–	0.08	0.14	0.13	0.81***	0.34*
	Sleep	0.12	0.08	–	0.17	0.02	0.05	0.05
Day 12	Mania	0.24	0.14	0.17	–	0.59***	0.17	0.02
Day 24	Mania	0.12	0.07	0.04	0.59***	–	0.29	0.01
	Cognition	0.13	0.81***	0.34*	0.17	0.29	–	0.11
	Sleep	0.02	0.05	0.05	0.02	0.01	0.11	–
Placebo (N = 35)								
Baseline	Mania	–	0.20	0.12	0.37**	0.34**	0.23	0.03
	Cognition	0.20	–	0.43*	0.06	0.05	0.53**	0.03
	Sleep	0.12	0.43*	–	0.10	0.33	0.27	0.23
Day 12	Mania	0.37**	0.06	0.10	–	0.67***	0.12	0.37*
Day 24	Mania	0.34**	0.23	0.03	0.67***	–	0.34*	0.02
	Cognition	0.05	0.53**	0.03	0.12	0.34*	–	0.24
	Sleep	0.33	0.27	0.23	0.37*	0.02	0.24	–

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

cally significant correlations were observed to mania and sleep quality at every time point.

Sleep quality was unrelated to mania and cognition at every time point. At day 12, higher mania scores were associated with higher mania scores at day 24, but not to sleep and cognitive performance at every time point. At day 24, no statistically significant correlations were observed between mania, cognitive performance and sleep disturbances.

Placebo Condition

At baseline, higher mania scores were associated higher mania scores at day 12 and 24. Otherwise, no further statistically significant correlations were observed between mania, cognitive performance, and sleep disturbances at any time point. A higher cognitive performance was associated with higher sleep disturbances at baseline and a higher cognitive performance at day 24. As men-

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tioned, sleep and cognition were related, but sleep was unrelated to mania and cognition at every time point. At day 12, higher mania scores predicted higher mania scores and lower sleep disturbance at day 24. At day 24, as mentioned, higher mania scores were predicted by higher mania scores at day 12. No further statistically significant correlations were observed between mania, cognitive performance, and sleep disturbances.

Discussion

The key findings of the present study were that among inpatients with diagnosed bipolar disorder in an acute manic phase and undergoing standard medication treatment with lithium, adjuvant levetiracetam improved symptom severity, and subjective sleep (medium to large effect sizes), while no further adjunctive improvements were observed for cognitive performance, always compared to placebo. The present results expand upon the sparse and timely literature on the possible effect of adjuvant levetiracetam in the treatment of manic states in individuals with bipolar disorder in 3 important ways. First, compared to previous studies (Ns between 1 and 25), we assessed a larger sample size (N = 72); second, compared to previous studies (case studies; not-blind intervention studies with no control conditions), the present study was a double-blind, placebo-controlled clinical trial; third, compared to previous studies (assessment of exclusively mania scores), we assessed also participants' cognitive performance, as assessed by experts, along with subjective sleep quality. Overall, the pattern of results suggests that adjuvant levetiracetam to lithium should be considered to enhance the treatment efficacy. Given the sparse and controversial results on the influence of levetiracetam on symptoms of mania and sleep and cognitive performance, not hypotheses, but research questions were formulated.

With the first research question we asked, whether levetiracetam adjuvant to lithium improved symptoms of mania, compared to placebo, and the answer was yes (see Tables 2, 3). Thus, we confirmed what has been sparsely reported in case and small-scale studies [26, 28, 29, 54], while the results are in contrast to a small-scale randomized study to compared levetiracetam to sodium valproate [30]. However, we expanded upon previous findings in 2 ways: The sample was quite large and data were gathered from a double-blind, placebo-controlled clinical trial. As such, we claim that the data quality is robust.

With the second research question we asked if compared to placebo, adjuvant levetiracetam improved dimensions of sleep disturbances, and the answer was yes again (see Tables 2, 3). With the third and last research question we asked, if compared to placebo, adjuvant levetiracetam improved the cognitive performance, and the answer was no (see Tables 2, 3).

Thus, while the pattern of results showed that adjuvant levetiracetam improved symptoms of mania and sleep disturbances, the quality of the data did not allow the understanding as to why this could be explained. To explain the effect of levetiracetam on mood and behavior, it appears that levetiracetam binds to the vesicle-glycoprotein SV2A [55]. As a result, lower concentrations of glutamate are freed from the presynaptic vesicles. Further, it is assumed that levetiracetam inhibits presynaptic calcium channels, leading to 2 major changes. It reduces the presynaptic neurotransmitter release and it impedes the impulse conduction across synapses [56, 57], and most probably also down-regulates cellular firing rates [58]. Overall, these neurophysiological concepts might explain the downregulated excitatory neuronal state among individuals with bipolar disorder during their manic state.

We further hold that such neurophysiological processes might explain why also sleep disturbances decreased over time in the levetiracetam condition, compared to the placebo condition. However, again, the quality of the data did not allow the introspection into the underlying neurophysiological process. As such, it remained unclear, if levetiracetam had a direct effect on the sleep-wake-promoting brain centers and concomitant neurophysiological processes [59, 60], or if levetiracetam impacted on improved sleep via the decrease of symptoms of mania. We further note that sleep also improved in the placebo condition; as such, it is also highly conceivable that improved sleep was an expected byproduct of patients' treatment regimen as inpatients recovered in a psychiatric ward. More specifically, and by nature, treatment regimen in psychiatric wards confer to a more stabilized and thoroughly supervised sleep-wake pattern, which in turn is associated with nighttime and daytime. Likewise, although again admittedly highly speculatively, more structured and thoroughly monitored sleep-wake-daytime activities might have further improved participants' mental stability.

The lack of levetiracetam-related cognitive improvements deserves further attention. As shown in Table 4, effect sizes of cognitive improvements from baseline to the end of the study were large both in the levetiracetam and in the placebo condition; in parallel, at the end of the

study, cognitive improvements did not differ between the 2 study conditions. Further, as shown in Table 5, cognitive improvements were unrelated to symptoms of mania and sleep disturbances, both cross-sectionally and longitudinally. In our opinion, this pattern of results reflects well what is already known from longitudinal studies [61, 62]: Even in remission as regards symptoms, functional and cognitive impairment appeared to persist, such that functional and cognitive recovery was delayed, when compared to symptomatic recovery. Given this, we claim that already during the pharmacologic treatment of manic states, cognitive performance lagged behind symptom recovery.

Despite the novelty of the results, the following limitations should be considered. First, inclusion and exclusion criteria were such to assess individuals with bipolar disorder without concomitant substance use, or without concomitant use of further stimulants and mood- and sleep-altering medications; however, experience of everyday clinical work with individuals with bipolar disorder show that such "clean" individuals are the exception and not the standard. As such, transferability of the present results to everyday clinical work should be done with caution. Second, the time frame of the study was set at 24 days; a longer term assessment might have allowed further insights as regards progression of symptoms, cognition and sleep. Third, to assess the cognitive performance, we used the MMSE [49], which is rather a coarse-grained screener; assessing dimensions of working memory, long-term memory of executive functions might have allowed a more detailed investigation of cognitive processes. Fourth, a major issue of individuals with bipolar disorder is their psychosocial impairment; as such, it would have been interesting to investigate, if adjuvant levetiracetam impacted favorably on social behavior. Fifth, to counterbalance issues related to dropouts and attrition, instead of 64 participants, we included 84 participants at baseline. A total of 72 participants completed the study; thus, the sample size still allowed detection of statistically significant mean differences. Next, a total of 5 individuals dropped in the levetiracetam, and 7 individuals dropped in the control condition, or the other way around: Dropout rate was quite balanced between the 2 groups. Accordingly, the decision was to perform the statistics per protocol, while the intent-to-treat with the last observation carried forward might have yielded further results.

Conclusions

Over a time lapse of 24 days, symptoms of mania and subjective sleep improved, but more so in the adjuvant levetiracetam condition, compared to placebo. Cognitive performance improved over time, but such improvements were unrelated to levetiracetam.

Statement of Ethics

All participants gave their signed written informed consent. This study with the code IRCT20120215009014N295 Clinical trial has been approved by the Research Ethics Committee of the Hamadan University of Medical Sciences (Hamadan, Iran).

Conflict of Interest Statement

All authors declare no conflicts of interest.

Author Contributions

Amir Keshavarzi, Aziz Sharifi, Leila Jahangard, Alireza Soltanian, Annette Beatrix Brühl, Mohammad Ahmadpanah, and Serge Brand contributed to the study setup and methodology. Amir Keshavarzi, Aziz Sharifi, Leila Jahangard, Alireza Soltanian, and Mohammad Ahmadpanah contributed to data gathering and data entry. Amir Keshavarzi, Aziz Sharifi, Leila Jahangard, Alireza Soltanian, Mohammad Ahmadpanah, and Serge Brand performed the data analysis. Amir Keshavarzi, Aziz Sharifi, Leila Jahangard, Alireza Soltanian, Annette Beatrix Brühl, Mohammad Ahmadpanah, and Serge Brand contributed to writing – draft and final manuscript.

Data Availability Statement

Data might be made available to experts in the field upon request and upon the detailed description of the reason of request.

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