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REGULAR ARTICLE

Efficacy and safety of palmitoylethanolamide as an adjunctive treatment for acute mania: A randomized, double-blind, placebo-controlled trial

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Aim: Palmitoylethanolamide is an endogenous fatty acid amide with neuroprotective and anti-inflammatory actions. We performed a randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy and safety of palmitoylethanolamide combination therapy in acute mania.

Methods: Patients in the acute phase of mania were assigned into two parallel groups given either lithium (blood level of 0.8–1.1 mEq/L) and risperidone 3 mg plus palmitoylethanolamide 600 mg or placebo twice per day for 6 weeks. All participants were assessed with the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), and Extrapyramidal Symptom Rating Scale (ESRS) at baseline and at weeks 1, 2, 4, and 6.

Results: A total of 63 patients (32 in palmitoylethanolamide and 31 in placebo groups) completed the trial. We found a significant effect for time×treatment interaction on the YMRS score ($F = 5.22$, d.f. $= 2.34$, $P = 0.004$) from baseline to study end point. Results from independent t test showed a significantly greater decrease in YMRS scores in the palmitoylethanolamide group, compared with the placebo group, from baseline to weeks 4 and 6 ($P = 0.018$ and $P = 0.002$, respectively). There was no significant difference between palmitoylethanolamide and placebo groups based on ESRS scores or ESRS changes in scores ($P>0.05$).

Conclusions: Our findings provide preliminary evidence that palmitoylethanolamide is an effective adjunctive medication that improves manic symptoms and overall clinical status in acute episodes of mania. However, larger sample sizes and more extended follow-up therapy are needed in future studies to confirm our findings.

Keywords: *acute mania, bipolar disorder, neuroinflammation, palmitoylethanolamide, peroxisome proliferator-activated receptor.*

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Bipolar disorder (BD) is a chronic psychiatric illness accounting for 1.3% of years lived with disability globally in 2013.[1] The diagnosis of BD is based on the occurrence of manic episodes (excessively elevated mood) in association with depressive ones.[2] Irritability, mood and humor elevation, insomnia, and high-risk activities (gambling and drug abuse) are all connected with acute mania, which can lead to cognitive deficits, hospitalizations, and eventually suicide.[3] In recent years, multiple underlying mechanisms have been proposed to explain BD pathophysiology, with inflammatory processes and oxidative stress receiving much attention.[3] It has been proven that manic and depressive episodes are linked to a proinflammatory state involving both the innate and adaptive immune systems. In this regard, tumor necrosis factor α (TNF-α) and interleukin (IL) 6 levels (as inflammatory cytokines) have been found to be elevated in patients with BD experiencing manic episodes.[4] Antipsychotic medication, lithium, anticonvulsants, and/or benzodiazepines are being used to treat BD in the acute manic phase. Nonetheless, there is considerable doubt regarding the most effective therapy. Since these drugs have a number of side effects including tiredness, poor cognition, mood changes, and metabolic imbalance, developing innovative therapeutic strategies for acute mania has gained attention in recent years.[3]

Palmitoylethanolamide is an endogenous acylethanolamide that is produced when needed from membrane phospholipids.[5] For the first time, it was extracted from purified lipid fractions of soybeans, egg yolk, and peanut meal.[6] High levels of palmitoylethanolamide exist in the central nervous system and are synthesized in large quantities by glial cells.[7] In a study conducted by Artomonov et al.,[8] the presence of labeled palmitoylethanolamide in rat's brain, after oral administration, indicated the compound's potential to permeate the blood–brain barrier, even if in small concentrations. Previously, it was hypothesized that palmitoylethanolamide was a cannabinoid receptor 2 agonist; however, Lo Verme et al.[9] demonstrated that palmitoylethanolamide had no impact on cannabinoid receptor 2 knockout mice. It is now well accepted that the principal pharmacological actions of palmitoylethanolamide are mediated through activation of the peroxisome proliferator-activated receptor (PPAR). PPARs are gene network regulators that control pain and inflammation by inhibiting the nuclear factor-B signaling cascade, a crucial component in gene transcription, resulting in creation of proinflammatory mediators.[5] A robust bulk of evidence has substantiated that palmitoylethanolamide is antiinflammatory,[10] analgesic in inflammation[11] and neuropathic pain,[12] inhibits food intake[13] and

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gastrointestinal motility,[14] suppresses cancer cell proliferation,[15] is antipruritic,[16] antiepileptic,[17] neuroprotective, antidepressant, and anxiolytic.[18,19] Although there is no animal or human study on the antimanic effects of palmitoylethanolamide, preclinical and clinical evidence has shown its strong antidepressant effects. In a recent study, the antidepressant-like effect of palmitoylethanolamide was investigated in male adult Kunming mice.[20] Oral palmitoylethanolamide has led to significant reduction in immobility in both tail-suspension and forced swimming tests without a significant change in motor activity.[20] Effects of palmitoylethanolamide were comparable to those produced by fluvoxamine in the control group.[20] Previous clinical trials in mood disorders such as depression[21] showed that palmitoylethanolamide has clinically significant antidepressant effects in patients with unipolar and bipolar depression, patients with resistant unipolar and bipolar depression, and patients with residual depressive symptoms.

To the best of our knowledge, there is no clinical study on the beneficial effects of palmitoylethanolamide on manic symptoms in patients with BD. This is the first randomized, double-blind, placebo-controlled clinical trial evaluating the effects of palmitoylethanolamide as an adjunctive treatment with lithium and risperidone in the management of acute mania in patients with BD.

Methods

Trial design and setting

This randomized, double-blind, placebo-controlled clinical trial was performed in inpatients with acute mania at Roozbeh Psychiatric Hospital (Tehran University of Medical Sciences, Tehran, Iran) and Razi Hospital (University of Social Welfare and Rehabilitation Sciences, Tehran, Iran) from May 2021 to January 2022. The primary comparison in this trial was between parallel palmitoylethanolamide and placebo groups. Patients were examined at five independent sessions: at baseline and at weeks 1, 2, 4, and 6. They were free to leave the trial at any time without providing a reason. Written informed consent was obtained before participation in the trial from patients and/or their legal guardians. The institutional review board of Tehran University of Medical Sciences approved the protocol for this study (IR.TUMS.DDRI.REC.1399.052). The study was in accordance with the Declaration of Helsinki and its subsequent revisions. The present study is registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT20090117001556N135).

Participants

The target population included male and female inpatients aged 18 to 54 years who had been diagnosed with BD and manic episodes based on the Structured Clinical Interview for *DSM-5* Disorders and the Mini International Neuropsychiatric Interview. At the time of randomization, participants had to be experiencing a moderate to severe episode of mania, as indicated by a Young Mania Rating Scale (YMRS) score of equal to or greater than 20. The aforementioned scale was composed of 11 components, each with five specified severity levels of the manic phase in BD.[22] The following were the exclusion criteria of the study: (i) IQ less than 70; (ii) history of allergy to lithium, risperidone, or palmitoylethanolamide; (iii) substance dependence (except nicotine and caffeine); (iv) receiving medications that cause manic-like symptoms, such as stimulants; (v) lactation or pregnancy; (vi) cardiac conduction disturbance; (vii) metabolic disorders such as hyperthyroidism or hypothyroidism; and (viii) severe hepatic disease. These exclusion criteria were ruled out via physical examination and electrocardiographic study.

Interventions

Patients who met the eligibility criteria were randomly assigned into either the palmitoylethanolamide or placebo groups. The palmitoylethanolamide group was treated with lithium, 3 mg risperidone and 600 mg palmitoylethanolamide (ACER, Tehran, Iran) twice per day, while the control group received lithium, 3 mg risperidone and placebo (ACER, Tehran, Iran) twice per day. Simultaneous administration of lorazepam (0.5 mg) was also permitted to manage symptoms including agitation, irritability, restlessness, insomnia, or hostility. Lithium was initiated at 300 mg per day and then increased to reach the therapeutic blood level of 0.8 to 1.1 mEq/L in 10 days. Risperidone was initiated at 1 mg daily and then increased to 3 mg daily in a week. Use of any psychotropic drugs or electroconvulsive therapy was prohibited for all participants during the trial. Patients were discharged when they became stable and continued treatment in the outpatient setting.

Outcomes

After recording the baseline demographics and characteristics, all patients were assessed with YMRS and Extrapyramidal Symptom Rating Scale (ESRS) at baseline and weeks 1, 2, 4, and 6 by two raters with acceptable inter-rater reliability for YMRS and ESRS (intraclass correlation coefficient = 0.90). YMRS is one of the most used rating scales to examine manic symptoms. ESRS is used to evaluate four different types of drug-induced movement disorders including parkinsonism, akathisia, dystonia, and tardive dyskinesia.[23] Patients were also examined with the 17-item HDRS (HDRS-17) at baseline and week 6. HDRS-17 is the most extensively used depression diagnostic scale delivered by a therapist. The average reduction of YMRS scores from baseline to the study end point between the two treatment groups was the primary outcome measure. ESRS scores and side effects were the secondary outcome measures of the study. At each appointment, adverse events were recorded using both ESRS scores and open-ended questions and a comprehensive side effect checklist that included general side effects and known adverse events of lithium, risperidone, and palmitoylethanolamide.[24] HDRS scores were reported to make sure that participants were not in a depressive episode.

Sample size

Based on our pilot study, a difference of 3 on the YMRS score between the palmitoylethanolamide and placebo groups with an SD of 3 was assumed. Considering a power of 85%, and a two-sided significance level of 5%, a minimal sample size of 40 was estimated. Considering an attrition rate of 20%, a total sample size of 50 (25 patients in each treatment group) was planned.

Randomization, allocation, concealment, and blinding

A digital random number generator was used to randomize patients via block randomization in a 1:1 ratio and a block size of four. The randomization process was implemented by an independent individual who was not involved in other sections of the trial. Patients, research investigators, nurses, and interviewers were all blinded to treatment allocation using sequentially numbered packages containing palmitoylethanolamide or placebo tablets. Palmitoylethanolamide and placebo tablets were identical regarding size, color, shape, texture, and odor.

Statistical analysis

SPSS version 21 (IBM) was used to analyze the data. Continuous and categorical variables were expressed as mean (SD) and frequencies (percentage), respectively. An independent *t* test was used for comparison of continuous variables between the two study groups. Chi-square and Fisher exact tests were used to compare categorical variables when appropriate. General linear model repeated-measures analysis was used to assess effect of time, treatment group (palmitoylethanolamide versus placebo), and time×treatment interaction on YMRS scores. If Mauchly test of sphericity was significant, a Greenhouse–Geisser adjustment in degrees of freedom was made. A *P*-value of <0.5 was considered statistically significant.

Results

Participants and baseline characteristics

A total of 105 patients were screened against the eligibility criteria; finally, 70 patients were included and randomized equally into two groups receiving either lithium + risperidone + palmitoylethanolamide (n = 35) or lithium + risperidone + placebo (n = 35). Three patients in the palmitoylethanolamide group and four patients in the placebo group were excluded before week 1 because of COVID-19 infection (Fig. 1) (Appendix S1). Finally, 32 patients in the palmitoylethanolamide group and 31 patients in the placebo group were analyzed. Table 1 demonstrates the baseline characteristics of patients in the two study groups. There was no significant between-group difference in age, sex, education, smoking, and marital status. The overall mean duration of BD was 5.59 years (SD, 5.16 years) and 6.41 years (SD, 6.04 years) for the palmitoylethanolamide and placebo groups, respectively (P= 0.562). Moreover, the baseline YMRS, HDRS, and ESRS scores were not significantly different between the palmitoylethanolamide and placebo groups (P= 0.516, 0.460, and 0.539, respectively).

Outcomes

YMRS and HDRS scores

Findings from general linear model repeated-measures showed significant effect for time×treatment interaction on the YMRS score (F = 5.22, d.f. = 2.34, P = 0.004) from baseline to the study end point. Results from independent t test showed a significantly greater decrease in YMRS scores in the palmitoylethanolamide group, compared with the placebo group, from baseline to week 4 (P = 0.018) and week 6 (P = 0.002) (Table and Fig. 2). However, the changed score from baseline to week 2 was not significantly different between trial groups. Moreover, at week 6, the YMRS score was significantly lower in the palmitoylethanolamide compared with the placebo group (P = 0.004). Both palmitoylethanolamide and placebo groups showed significant improvement in YMRS scores from baseline to the study end point (P<0.001).

Results from independent t test demonstrated a significant difference in HDRS score at week 6 between trial groups, with lower scores in the placebo group (P = 0.030) (Table 2). However, the change in score of HDRS from baseline to week 6 was not significantly different between trial groups.

ESRS score

General linear model repeated-measures found no significant effect for time×treatment interaction on ESRS score (F = 1.94, d.f. = 3.07, P = 0.122) from baseline to study end point (Fig. 3). As shown in Table 2, there was no significant difference between the palmitoylethanolamide and placebo groups based on ESRS scores or ESRS changes in scores (P>0.05).

Adverse effects

As shown in Table 3, no significant between-group difference was found regarding the frequency of adverse events. Dizziness (18.75%) was the most frequent adverse event in the palmitoylethanolamide group, while dizziness (16.1%), drowsiness (16.1%), and increased appetite (16.1%) were the most frequent adverse events in the placebo group. No unforeseen sign or symptom was reported by the study participants. No serious adverse event/death occurred.

Discussion

This is the first randomized, double-blind, placebo-controlled clinical trial, to our knowledge, that examines the possible adjuvant effects of palmitoylethanolamide in pharmacological therapy of acute mania in patients with BD. The therapeutic effect of palmitoylethanolamide on acute mania was evaluated using the YMRS score as the primary outcome measure and ESRS/side effects as the secondary outcome measure. Our findings demonstrate that adding palmitoylethanolamide to the treatment regimen of patients with BD improves manic symptoms

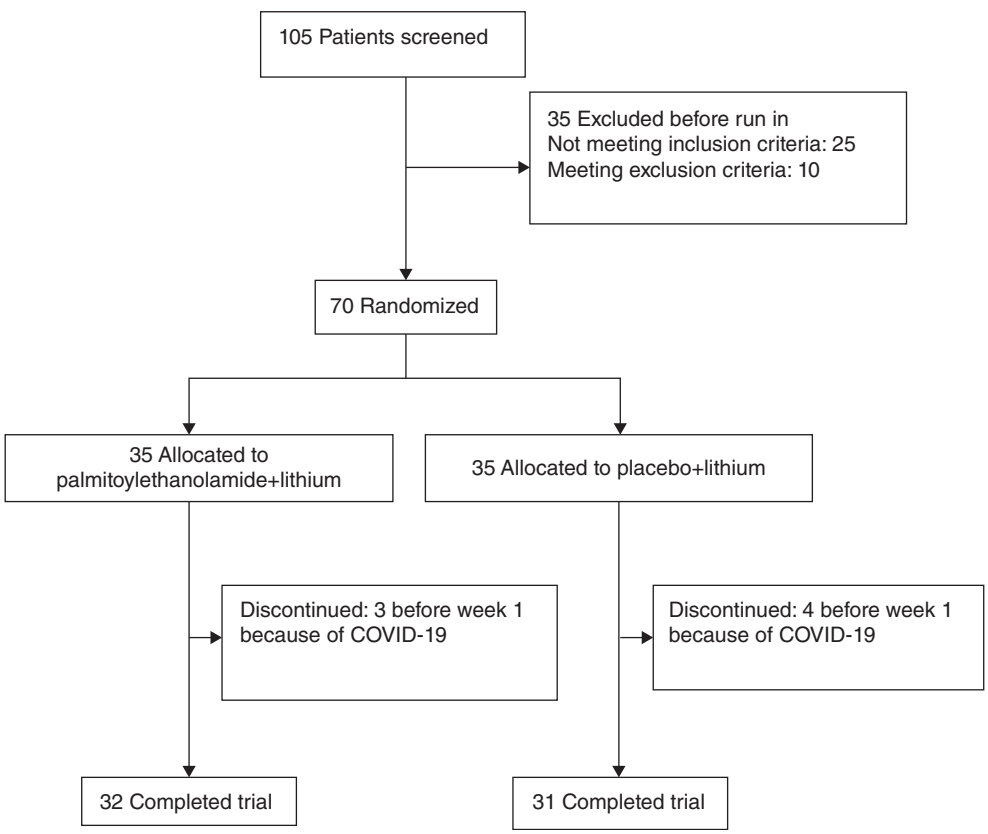

Fig. 1 Flow diagram of the study.

Table 1. Baseline characteristics of the patients in the two trial groups

	Palmitoylethanolamide group (n = 32)	Placebo group (n = 31)	*P*-value
Age, mean (SD) (years)	30.78 (9.80)	32.74 (9.04)	0.413†
Sex, n (%)			0.530‡
Male	23 (71.9)	20 (64.5)	
Female	9 (28.1)	11 (35.5)	
Education, n (%)			0.970‡
Illiterate	5 (15.6)	6 (19.4)	
Primary	6 (18.8)	6 (19.4)	
Secondary	6 (18.8)	7 (22.6)	
Diploma	12 (37.5)	10 (32.3)	
University	3 (9.4)	2 (6.5)	
Smoking (yes), n (%)	12 (37.5)	9 (29)	0.476‡
Marital status, n (%)			0.826‡
Single	14 (43.8)	12 (38.7)	
Married	12 (37.5)	14 (45.2)	
Separated	6 (18.8)	5 (16.1)	
Overall duration of bipolar disorder, mean (SD) (years)	5.59 (5.16)	6.41 (6.04)	0.562†
Baseline HDRS score, mean (SD)	6.81 (1.49)	7.06 (1.56)	0.516†
Baseline YMRS score, mean (SD)	31.34 (7.63)	29.96 (7.01)	0.460†
Baseline ESRS score, mean (SD)	0.46 (1.62)	0.25 (0.99)	0.539†

$P<0.05$ was considered statistically significant.
†Student *t* test.
‡Chi-square test.
ESRS, Extrapyramidal Symptom Rating Scale; HDRS, Hamilton Depression Rating Scale; YMRS,Young Mania Rating Scale.

4 and 6 weeks after treatment. In addition, adjunctive treatment with palmitoylethanolamide is not associated with increased ESRS scores or adverse events.

The exact pathophysiology of acute mania in BD is not well understood. Multiple underlying pathogenic pathways have been proposed to contribute to the acute phase of mania in BD. However, immune dysfunction is significantly linked to BD. Anti-inflammatory drugs have been shown to have a favorable effect on BD in numerous proof-of-concept clinical trials, with generally good tolerability.[25] In accordance, a systematic review was published in 2017[26] in which inflammatory biomarkers were suggested to have a role in BP. During the early stages of BD, peripheral proinflammatory indicators and nitration-induced damage generated systemic toxicity that improved with treatment.[27] Cytokines are small secretory proteins that control how our bodies react to infections, immunological responses, inflammation, and trauma.[28] Cytokines have the potential to affect serotonin-catecholamine–related circuits in the brain, resulting in mood alterations. Cytokines, like neurotransmitters and hormones, may maintain homeostasis in the hypothalamus–pituitary–adrenal axis in response to stresses. Since both the immune system and the hypothalamus–pituitary–adrenal axis appear to be harmed in BD, cytokines may play a significant role.[29] When patients with BD in manic and depressed phases were compared with healthy controls, researchers discovered a proinflammatory state with high levels of proinflammatory cytokines and low levels of anti-inflammatory ones.[30] There was an increase in TNF-α, IL-6, and IL-10 levels compared with controls. Even in the late phases, TNF-α and IL-6 showed similar increases although IL-10 did not. This late-stage rise in cytokines could be attributed to BD's poor inflammatory systems.[31] We hypothesize that the beneficial effects of palmitoylethanolamide on manic symptoms of patients with BP might be through modulation of inflammatory markers. However, we did not measure cytokines in our population. Further studies could assess this hypothesis.

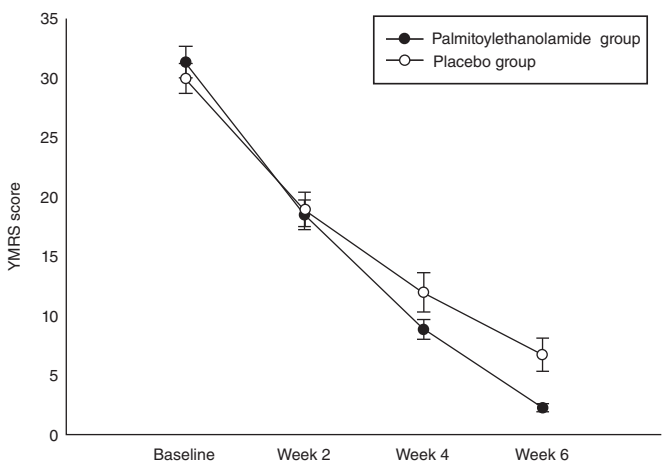

Fig. 2 Comparison of mean in Young Mania Rating Scale (YMRS) scores between the palmitoylethanolamide and placebo groups. Error bars show SEM.

The pharmacokinetics of palmitoylethanolamide in humans is poorly understood and the bioavailability and apparent distribution volume in patients with BD have not been investigated.[32] Nonetheless, limited publications were found measuring palmitoylethanolamide serum levels in different circumstances. When compared with healthy controls, children and adolescents with autism spectrum disorder have lower palmitoylethanolamide levels in their

Table 2. Comparison of scores and score changes between the two trial groups

	Clinical scores	Palmitoylethanolamide group (n = 32)	Placebo group (n = 31)	*P*-value
YMRS	Baseline	31.34 (1.34)	29.96 (1.26)	0.460
	Week 2	18.50 (1.25)	18.93 (1.46)	0.822
	Week 4	8.87 (0.83)	11.96 (1.65)	0.101
	Week 6	2.28 (0.32)	6.74 (1.41)	**0.004**
	Change from baseline to week 2	−12.84 (1.34)	−11.03 (1.40)	0.355
	Change from baseline to week 4	−22.46 (1.21)	−18.00 (1.38)	**0.018**
	Change from baseline to week 6	−29.06 (1.28)	−23.22 (1.27)	**0.002**
HDRS	Baseline	6.81 (0.26)	7.06 (0.28)	0.516
	Week 6	5.78 (0.33)	4.83 (0.26)	**0.030**
	Change from baseline to week 6	−1.03 (0.48)	−2.22 (0.40)	0.064
ESRS	Baseline	0.46 (0.28)	0.25 (0.17)	0.539
	Week 1	1.09 (0.32)	0.64 (0.28)	0.304
	Week 2	2.53 (0.28)	1.80 (0.24)	0.061
	Week 4	2.68 (0.31)	2.80 (0.27)	0.778
	Week 6	2.59 (0.27)	3.29 (0.42)	0.170
	Change from baseline to week 1	−0.62 (0.46)	−0.38 (0.29)	0.670
	Change from baseline to week 2	−2.06 (0.43)	−1.54 (0.31)	0.346
	Change from baseline to week 4	−2.21 (0.43)	−2.54 (0.26)	0.520
	Change from baseline to week 6	−2.12 (0.41)	−3.03 (0.42)	0.132

P<0.05 was considered statistically significant. Data are shown as mean (SEM). Bold values indicate significance.
ESRS, Extrapyramidal Symptom Rating Scale; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

blood.[33] However, if animal models closely resemble clinical human findings, palmitoylethanolamide levels rise either systemically or regionally in the face of neuropathic injury and inflammation.[34] Interestingly, in 2021, a study provided the first evidence that the endocannabinoid system mediates the link between gut microbial diversity and anhedonia.[35] Reduced microbial diversity was associated with increased fecal excretion of the endocannabinoid (palmitoylethanolamide), which is considered a sign of an "unhealthy" microbiome and has been related to a variety of negative health outcomes, including psychosis and depression.[36] As a result, it would be intriguing to conduct more research using biological samples (eg, blood and feces).

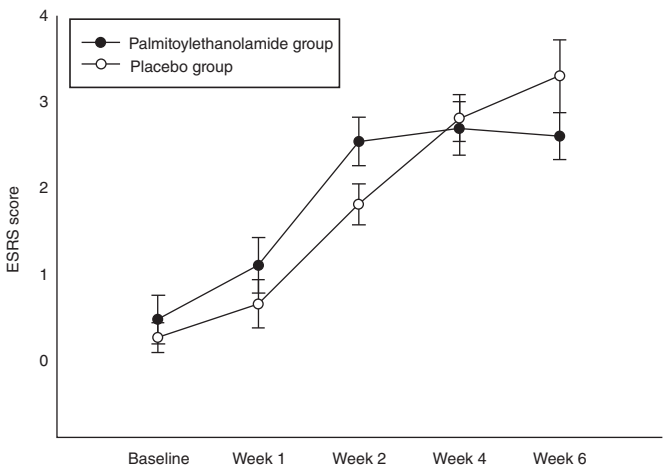

Fig. 3 Comparison of mean Extrapyramidal Symptom Rating Scale (ESRS) scores between the palmitoylethanolamide and placebo groups. Error bars show SEM.

Currently, there is no clinical study investigating the antimanic effects of palmitoylethanolamide. However, effects of palmitoylethanolamide on depression have been studied. Ghazizadeh-Hashemi et al.[37] performed the first human trial to investigate the antidepressant potential of palmitoylethanolamide (600 mg twice daily) as an additional treatment to the standard antidepressant citalopram. HDRS scores improved significantly in the palmitoylethanolamide group over the course of the experiment. Palmitoylethanolamide has also been studied as a possible biomarker in stress and depression. In a study of 15 medication-free women with major depressive disorder, blood levels of palmitoylethanolamide were found to be equal to those of 15 age-matched healthy controls, and 30 minutes after exposure to social stress, serum levels of palmitoylethanolamide decreased in both groups.[38] Rise in palmitoylethanolamide following stress was positively linked with increases in serum cortisol, highlighting the close relationship between palmitoylethanolamide and stress hormones.[39] To dig deeper, Raso and colleagues[40] showed that PPAR-α and its putative endogenous ligand, palmitoylethanolamide, can regulate neurosteroidogenesis in astrocytes, which, like other glial cells and neurons, have the enzymatic machinery for de novo production of neurosteroids. The enzyme itself can transform cholesterol into pregnenolone, the main precursor of neuroactive hormones. Furthermore, PPAR-α influences excitatory glutamatergic neurotransmission as well as cholinergic/dopaminergic signaling in the brain and regulates oxidative stress, energy homeostasis, and mitochondrial fatty acid metabolism.[41] Interestingly, the data from Esmaeili et al.[42] demonstrated that preferential activation of PPAR-α by fenofibrate reduces neuroinflammation and blocks neurodegeneration in the mouse model of amyotrophic lateral sclerosis. It also downregulates the expression of genes that are involved in neuroinflammation. Although this evidence cannot be directly compared with our findings, they might reveal potential mechanisms via which palmitoylethanolamide improves mania. Moreover, palmitoylethanolamide has recently gained popularity[43] as a result of its interaction with the endocannabinoid system, a

Table 3. The frequency of adverse events in the study populations

Side effect	Palmitoylethanolamide group (n = 32)	Placebo group (n = 31)	*P*-value*
Drowsiness	4 (12.5)	5 (16.1)	0.67
Dizziness	6 (18.75)	5 (16.1)	1.00
Increased appetite	4 (12.5)	5 (16.1)	0.67
Rash	3 (9.3)	2 (6.4)	1.00
Diarrhea	4 (12.5)	3 (9.6)	1.00
Dry mouth	4 (12.5)	3 (9.6)	1.00
Sore throat	2 (6.25)	1 (3.2)	1.00
Tachycardia	3 (9.3)	2 (6.4)	1.00

$P<0.05$ was considered statistically significant. Values are expressed as number (percentage).
*Fisher exact test was used for comparison of all adverse events.

neuromodulator of the central and peripheral nervous systems and a key mood regulator[44] that we believe can affect both depression and mania treatments.

The current study has certain limitations, First, since our sample size was small, larger studies with larger sample sizes should be conducted to examine the potential effects of add-on palmitoylethanolamide treatment on the acute phase of mania, Second, the main focus of this study was the manic phase of BD, and the potential effects of palmitoylethanolamide on the depressive phase of BD were not investigated. Third, because of the add-on nature of our clinical trial, there is no evidence for the effects of palmitoylethanolamide monotherapy on manic symptoms of BD, and palmitoylethanolamide monotherapy was avoided because of ethical concerns. Finally, routine laboratory tests were not provided in this study, which could have helped detect the mechanisms through which palmitoylethanolamide improves mania.

In conclusion, multiple lines of evidence imply that palmitoylethanolamide can be a potent anti-inflammatory drug with multiple neuroprotective characteristics that could be useful in therapeutic settings.[44-46] This is the first randomized, double-blind, placebo-controlled clinical trial, to our knowledge, that examines the possible adjuvant effects of palmitoylethanolamide in pharmacological therapy of acute mania in patients with BD. We observed that adjunctive palmitoylethanolamide treatment results in considerable improvements in manic symptoms and overall clinical status in acute mania. While this is the first study to measure the effects of palmitoylethanolamide on BD manic symptoms, validation of its therapeutic effects in larger-scale trials could lead to its inclusion as an effective add-on treatment for the acute phase of mania.

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Disclosure statement

The authors declare no conflicts of interest.

Author contributions

T.A, R.H., F.G., and H.S.M. participated in data acquisition and the preparation of the manuscript. S.A., M.R.K.A, and A.T. designed the manuscript, provided the outlines for presentation of the study, supervised the study process, and edited the final manuscript. All authors have reviewed the process of data analysis, writing of the manuscript, and approved the final article.

Data Availability Statement

Individual participant data will be shared upon request.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supporting Information