Journal of Affective Disorders 232 (2018) 127–133

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial

Maryam Ghazizadeh-Hashemi[a,1], Alireza Ghajar[b,1], Mohammad-Reza Shalbafan[a,1], Fatemeh Ghazizadeh-Hashemi[a], Mohsen Afarideh[b], Farzaneh Malekpour[a], Ali Ghaleiha[c], Mehrdad Eftekhar Ardebili[a], Shahin Akhondzadeh[b,*]

[a] Mental Health Research Center, Iran University of Medical Sciences, Tehran, Iran
[b] Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
[c] Research Center for Behavioral Disorders and Substance Abuse, Hamadan University of Medical Sciences. Hamadan, Iran

ARTICLE INFO

Keywords:
Anti-inflammatory
Glutamate
Major Depressive Disorder (MDD)
PPAR-α agonists
Palmitoylethanolamide (PEA)

ABSTRACT

Background: Experimental studies provide evidence for antidepressant effects of Palmitoylethanolamide (PEA) in animal models of depression. We aimed to evaluate the efficacy and tolerability of PEA add-on therapy in treatment of patients with major depressive disorder (MDD).

Methods: In a randomized double-blind, and placebo-controlled study, 58 patients with MDD (DSM-5) and Hamilton Depression Rating Scale (HAM-D) score ≥ 19 were randomized to receive either 600 mg twice daily Palmitoylethanolamide or placebo in addition to citalopram for six weeks. Patients were assessed using the HAM-D scale at baseline and weeks 2, 4, and 6.

Results: Fifty-four individuals completed the trial. At week 2, patients in the PEA group demonstrated significantly greater reduction in HAM-D scores compared to the placebo group (8.30 ± 2.41 vs. 5.81 ± 3.57, P = .004). The PEA group also demonstrated significantly greater improvement in depressive symptoms [F (3, 156) = 3.35, P = .021] compared to the placebo group throughout the trial period. The patients in the PEA group experienced more response rate (≥ 50% reduction in the HAM-D score) than the placebo group (100% vs. 74% respectively, P = .01) at the end of the trial. Baseline parameters and frequency of side effects were not significantly different between the two groups.

Limitations: The population size in this study was small and the follow-up period was relatively short.

Conclusions: Palmitoylethanolamide adjunctive therapy to citalopram can effectively improve symptoms of patients (predominantly male gender) with major depressive disorder. PEA showed rapid-onset antidepressant effects which need further investigation.

1. Introduction

Major depressive disorder (MDD), known as a high burden disability among mental and behavioral disorders, is within the top ten causes of all-age Disability Adjusted Life Years (DALYs) in high-income countries (Abajobir et al., 2017). Due to the relatively late onset of treatment effects and incomplete response to conventional antidepressants in patients with MDD, new efficacious augmentative medications have been targeted with caution (Fava, 2009). One of the proposed add-on treatments might be Palmitoylethanolamide (PEA), a naturally occurring amide of ethanolamine and palmitic acid with anti-inflammatory and endocannabinoid effects (Conti et al., 2002). Over the last two decades, increasing data has demonstrated that immuno-inflammatory biomarkers, including interleukin (IL)−1, IL-6, and tumor necrosis factor (TNF)-α, are present and involved in the pathogenesis of major depression (Anisman and Merali, 2002; Pariante, 2017). The interaction between these pro-inflammatory cytokines, prostaglandin (PG)-E2 production, and depressive symptoms have led to the hypothesis of anti-inflammatory agent utilization in the treatment of patients with MDD (Müller, 2013). Moreover, a growing body of evidence indicates that deficits in endocannabinoid system (ECS) signaling may result in neuropsychiatric disorders, mainly mood disturbances, while the augmentative therapeutic use of endocannabinoids is suggested to produce convincing results in affective disorders (Hill and Gorzalka, 2009; Micale et al., 2013). The N-methyl-D-aspartate (NMDA) receptors are also indicated to be involved in the circuits affecting mood disturbances, and targeting of NMDA receptors are becoming of interest in the treatment of depressive

* Corresponding author.
E-mail address: s.akhond@neda.net (S. Akhondzadeh).
[1] The first three authors contributed equally to this study.

https://doi.org/10.1016/j.jad.2018.02.057
Received 27 November 2017; Received in revised form 3 February 2018; Accepted 19 February 2018
Available online 21 February 2018

symptoms (Dang et al., 2014; Skolnick et al., 1996).

Even though high levels of PEA exist in the central nervous system, we have limited information about its mechanism of action (Paterniti et al., 2013b). PEA is an N-acylethanolamine (NAE), an endogenous fatty acid amide with different targets ranging from peroxisome proliferator-activated receptor alpha (PPAR-α) and cannabinoid-like G-coupled receptors to less discussed targets like NMDA receptors (Coppola and Mondola, 2013; Lambert et al., 2002; Skaper et al., 1996). PEA affects endocannabinoid (eCB) signaling through PPAR-α activation and affects indirect regulation of microglial cannabinoid (CB) type 2 receptor (CB2R) expression (Guida et al., 2017a). Moreover, several lines of evidence suggest beneficial effects of PEA as an anti-inflammatory (Benvenuti et al., 1968), analgesic (Calignano et al., 1998), anti-epileptic, and neuroprotective agent (Franklin et al., 2003). It's suggested that PPAR-α agonists might have therapeutic efficacy in treatment of mood disorders through regulation of dopamine (and possibly serotonin) neuron activity via nicotinic acetylcholine receptors (Melis et al., 2013). Glutamate transmission and its dysregulation are involved in depressive disorders (Sanacora et al., 2012). Meanwhile, PEA restores the glutamatergic synapse proteins and changes amino acid release (homeostasis) (Guida et al., 2015). In a late post glutamate paradigm of excitotoxic death in cultivated cerebellar granule neurons, PEA could be an endogenous protective mediator in NMDA induced neuronal death (Skaper et al., 1996).

PEA prevents the run-down of cortical spreading depression (CSD is a wave of neuronal depolarization in the cerebral cortex following traumatic brain injury or cerebral ischemia, which significantly aggravates brain damage) amplitudes, likely through inhibiting proinflammatory cytokine release (Richter et al., 2016). In a mouse model of traumatic brain injury (TBI), PEA showed improvements in neurological dysfunction by restoring cortical electrophysiological activity by normalizing the firing activity of the pyramidal neurons in the medial prefrontal cortex of 14-dayTBI mice (Guida et al., 2017b). PEA activates and desensitizes TRPV1 (transient receptor potential cation channel subfamily V member 1) channels. This effect is hypothesized to be facilitated at least in part by PPARα activation (Ambrosino et al., 2013). TRPV1, known as the capsaicin receptor, is expressed at high levels in the central nervous system and is involved in pain transmission and modulation (Cui et al., 2006). It has been suggested as a target for treatment of neuropsychiatric conditions such as anxiety aside from pain management (Marzo et al., 2008).

It is proposed that PEA might be a physiological endogenous compensatory factor in the body which increases naturally when a person is confronted with chronic pain and depressed feelings (Darmani et al., 2005). This hypothesis is strengthened with evidence showing that antidepressants like imipramine and escitalopram could increase the PEA levels in the brain (Smaga et al., 2014). Considering that both the endocannabinoid system and inflammation play key roles in the pathogenesis of depression, utilization of the natural substance PEA as an antidepressant agent seems reasonable (Coppola and Mondola, 2014). This idea is being supported by experimental studies demonstrating antidepressant effects of exogenous PEA in animal models of depression (Crupi et al., 2013; Yu et al., 2011).

To the best of our knowledge, current studies of PEA are mostly either experimental studies or pain related studies in human beings, and this is the first double-blind placebo-controlled study investigating the pure anti-depressant effects of PEA in patients with major depressive disorder. We hypothesized that onset of treatment effects and extent of symptom reduction in depression should be more pronounced in patients who received PEA.

2. Methods

2.1. Trial design and setting

This study was conducted as a two center, double-blind, parallel-group, randomized clinical trial at the outpatient clinic of Iran hospital and Tehran Psychiatric Institute from February 2017 to October 2017. The study was conducted in accordance with the latest revision of the Declaration of Helsinki. The trial protocol was registered at the Iranian registry of clinical trials (www.irct.ir; trial identifier with the IRCT database: IRCT201702181556N97) and was approved by the institutional review board (IRB) of the Tehran University of Medical Sciences' protocol (IR.TUMS.VCR.REC.1395.1624).

2.2. Trial participants

Eligible patients were men and women aged 18–50 years with a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (Structured Clinical Interview), Fifth Edition, (DSM-5), with a score of ≥19 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and with a score of at least 2 on item 1 of HAM-D. Exclusion criteria were as follows: Receipt of any antidepressant medication and psychotherapy treatments during the previous month; receipt of electroconvulsive therapy (ECT) during the last 2 months; presence of psychosis or diagnosis of other mental disorders; alcohol or substance (with the exception of nicotine) abuse or dependence within one year; high risk of suicide or suicidal ideation; any uncontrolled medical problem such as cardiovascular diseases, hypertension, thyroid disorders, or pregnancy. The participants were informed that withdrawal from the study, at any time, was allowed without compromising their relationship with their healthcare provider.

2.3. Interventions

Eligible patients randomly received either 600 mg twice daily PEA (ultra-micronized PEA; ACER, Tehran, Iran) or placebo in the same manner for 6 weeks. All participants received 40 mg/day citalopram (citalopram, Sobhan Darou, 20 mg capsules) during the course of the trial. Citalopram was administered at half dose in the first week. Patients were not treated with any other psychiatric or nonpsychiatric medication during the course of the trial. Weekly capsule counts were justified against participant reports of medication intake in order to measure medication adherence.

2.4. Outcomes

Participants were evaluated using HAM-D (Hamilton, 1960) 17-item rating scale at baseline and at weeks 2, 4 and 6 post-intervention that has been used in a number of trial in Iran (Modabbernia et al., 2012). Three senior psychiatrists were responsible for rating the patients with an inter-reliability of > 90% on HAM-D. The primary outcome measure was to evaluate the efficacy of PEA in improving the HAM-D score compared with placebo during the trial course using a general, linear, repeated-measures model. Score change (at each visit), response rates (defined as ≥ 50% reduction in the HAM-D score), remission rates (defined as HAM-D score ≤7) and time to response or remission were also compared between the two study groups (Zeinoddini et al., 2015; Kashani et al., 2017). Adverse events were systematically evaluated at each time point using a side-effect checklist (Noorbala et al., 1999; Akhondzadeh et al., 2000). This was further augmented by self-reports of the patients. Electrocardiography was performed if patients complained of any typical or atypical cardiac syndromes.

2.5. Sample size determination

A sample size of 52 (26 patients in each group) was calculated assuming a clinically significant difference of 3 on the HAM-D score, a standard deviation (SD) of 3, a two-sided significance level of 5%, and a power of 95%. Assuming a drop-out rate of 10% and to achieve a perfect score ratio of 1.0 for the placebo and PEA allocation groups, the final sample size of 58 was planned.