

Palmitoylethanolamide (PEA) as adjunctive therapy in major depressive disorder (MDD)

BACKGROUND:

- Palmitoylethanolamide (PEA) is an endogenous compound that has been studied in humans for its anti-inflammatory effects.
- PEA has demonstrated antidepressant effects in animal models of depression but has never been studied in humans for depression.

OBJECTIVE:

- To evaluate the efficacy of PEA as adjunct therapy in patients with major depressive disorder (MDD) as reflected by an improvement in the Hamilton Rating Scale for Depression (HAM-D) score compared to citalopram alone.

METHODS

- **Type of study design:** Double blind, randomized, placebo-controlled trial at 2 centers
- **Study duration:** 6 weeks
- **Important inclusion/exclusion criteria:**
 - Inclusion: age 18-50, have a diagnosis of MDD (DSM-5 criteria), HAM-D score ≥ 19 , and a score of at least 2 on item 1 of HAM-D
 - Exclusion: any antidepressant medication and psychotherapy treatment during previous month, electroconvulsive therapy during the last 2 months, presence of psychosis or diagnosis of other mental disorder, alcohol or substance abuse or dependence (not including nicotine) within one year, high risk of suicide or suicidal ideation, any uncontrolled medical problem, or pregnancy
- **Number of patients enrolled:** 58 patients randomized (29 per group)
- **Drug regimens/dosages used:** Every patient received citalopram 40mg daily (20mg during the first week) along with either PEA 600mg twice daily or placebo for 6 weeks
- **Outcome measures (efficacy and safety):** Efficacy: changes in the 17 item HAM-D rating scale at baseline and at 2, 4, and 6 weeks post intervention.
- **Power (if mentioned):** Power of 95% with a sample size of 52 patients, an effect size of 3 (change in HAM-D score), and a two-sided significance level of 5%.
- **Data handling method used:** Intent to treat with last observation carried forward

RESULTS

- 54 patients finished the study, 27 in each group
- The authors conclude that PEA is safe and significantly beneficial as adjunct therapy for people with major depressive disorder.

STRENGTHS

- This was a placebo-controlled, double-blind, randomized trial
- Citalopram is a well-established drug for the treatment of MDD

LIMITATIONS

- Females were not equally represented in the study population, only comprising 35%
- It was unclear what past antidepressant treatment the subjects had used
- Duration of treatment and observation was very short considering the therapy and disease state
- Initiating two treatments at the same time does not typically occur in practice so the clinical usefulness is limited based on the study approach
- The dosage of PEA was consistent with doses used for pain and inflammation in other studies. Other dosage of PEA could be explored

CONCLUSIONS

- Palmitoylethanolamide (PEA) is well tolerated but it is unclear if it could benefit patients with depression. The population being studied and the size of the study does not lend itself well to extrapolation to the general population. Furthermore the effect size of a change of 3 on the HAM-D score was not achieved between study and placebo groups
- PEA is available over the counter and is relatively inexpensive. However, it is certainly not going to displace any current treatments. Furthermore the content of over the counter medications is not regulated and variation between products is likely. An inadequate amount of information is available for PEA drug interactions, though some studies exist that state it interacts with tramadol and phenobarbital.
- Doses of up to 30mg/kg have been studied for acute respiratory tract infections under the name "Impulsin®" so there is room for dose escalation in future studies.
- Other studies could enroll patients who are stable on a treatment regimen but are not completely satisfied with the results and are at the maximum dose of their given treatment. In these patients PEA could be added instead of a second prescription option and their outcomes could be evaluated. This design could possibly make PEA a more viable option for patients being treated for depression depending on the results.

Ghazizadeh-Hashemi M, Ghajar A, Shalbafan MR, et al. Palmitoylethanolamide (PEA) as adjunctive therapy in major depressive disorder (MDD). *J Affect Disord.* 2018 May;232:127-133.

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