Randomized, Placebo Controlled Trial of the Fatty Acid Amide Hydrolase Inhibitor Palmitoylethanolamide in Bipolar Depression

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A Randomized, Placebo Controlled Trial of the Fatty Acid Amide Hydrolase Inhibitor Palmitoylethanolamide in Bipolar Depression

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Abstract: There is growing interest in the endocannabinoid system (ECS) as an alternative signaling pathway in the therapeutics of Mood Disorders. The ECS also modulates the rewarding properties of environmental stimuli, influencing synaptic transmission in the dopaminergic projections to the limbic system, and controls the neurophysiological and behavioral effects of stress. In response to stressors such as mood episodes, the breakdown of endocannabinoids is increased by the Fatty Acid Amide Hydrolase {FAAH) degrading enzyme located in the somatodendritic compartments of neurons, which reduces endocannabinoid levels and increases HPA stress and inflammation. A similar increase in FAAH breakdown has been described in subjects with depression, post-traumatic stress disorder and suicide ideation. Thus, FAAH inhibition may also represent a unique, valuable target in the therapeutics of depressive episodes in bipolar disorder (BD).

Palmitoylethanolamide (PEA) is a classic FAAH inhibitor. This member of the extended endocannabinoid family significantly increases the levels of key endocannabinoids (ECs) such as anandamide (AEA), 2-arachidonoylglycerol (2-AG) and oleoylethanolamide (OEA). PEA also activates CBl receptor through the called entourage effect PEA -induced increase in ECs levels induces potent anti-inflammatory and antioxidant effects in humans. In contrast, lower PEA levels have been described in depression, inversely associated with depressed mood, diminished interest/pleasure, and psychomotor retardation. The first clinical trial examining the antidepressant of PEA (600 mg twice daily for six weeks, double-blind, placebo-controlled design) in depression showed a significant improvement in depression scores compared to placebo. The PEA group showed rapid onset and significantly greater improvements in depressive symptoms score from week 2 compared to the placebo group.

The objective of this double-blind, placebo-controlled, 6-week study is to evaluate the antidepressant efficacy of the PEA in Bipolar Depression and the association between antidepressant response with endogenous cannabinoids and cytokine levels (ECs-- PEA, AEA, 2-AG, OEA; Cytokines-- TNF, IL2,4,6, 10,12). Outpatients with BD in a depressive episode will be followed up for six weeks, with baseline, week 2, 4, and endpoint (week 6) assessments. Two groups will be randomized: treatment as usual (TAU, mood stabilizer) plus placebo (n=25) versus TAU plus ultra-micronized PEA (PEA-um) (600mg twice daily) (n=25) PEA-um has shown high bioavailability and easily crosses the BBB, as demonstrated by the significant increase of PEA levels in the hippocampus, brain, and spinal cord after oral use. Our scientific environment will contribute to the success of this project since our group has extensive experience in clinical trials and biomarkers of BD. We trust that the proposed approach is highly innovative and may represent a unique opportunity to develop new, improved therapeutics for this devastating illness.

Project Summary: There is an unmet need for conducting more clinical studies testing molecules targeting new neurotransmitter systems in BD. The endocannabinoid system (ECS) controls neurotransmission, neuroendocrine, and inflammatory processes, mostly through effects mediated by

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the Fatty Acid Amide Hydrolase (FAAH). The FAAH inhibitor Palmitoylethanolamide (PEA) increases the levels of key endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG). PEA is the only available compound able to indirectly activate the ECS and enhance endocannabinoid levels. PEA has demonstrated robust antidepressant, anti-pain, and anti-inflammatory effects in clinical studies. In models of depression, increased breakdown of the classic endocannabinoid anandamide (AEA) by FAAH activates HPA stress, inflammation and impairs plasticity mostly by limiting endocannabinoid (CBl) signaling. Thus, tools able to significantly enhance AEA and EC levels may advance our understanding of mechanisms involved in the neurobiology of depression. The FAAH antagonist PEA represents a unique pharmacological tool to increase AEA levels and boost EC function, associated with antidepressant, anti-inflammatory and neurotrophic effects. We aim to evaluate and pharmacologically modulate the levels of endogenous cannabinoids as biomarkers of antidepressant response in BD. PEA has been shown to significantly increase AEA levels (10-15 times) in other conditions. We hypothesize that PEA activating effects at AEA levels and ECS activity will improve clinical symptomatology in bipolar depression and may represent an innovative system to be further explored in bipolar disorder (BD) research. Different from classic cannabinoids, our innovative approach focusing on the indirect activation of the cannabinoid system will help to avoid adverse effects, abuse, and liability. PEA has consistently shown safety in diverse clinical studies and being a nutraceutical, it has been associated with a very mild adverse effect profile. In the words of the Nobel Prize winner Rita Levi-Montalcini, "*The effects of Palmitoylethanolamide reflect the consequences of supplying the tissue with a sufficient quantity of its physiological regulator of cellular homeostasis*." Based on recent positive results in unipolar depression, our study aims to follow -up outpatients with BD in a depressive episode for six weeks in a double-blind, placebo-controlled design. Two groups will be randomized: treatment as usual (TAU, mood stabilizer) plus placebo (n=25) versus TAU plus ultra-micronized PEA (PEA-um) (600mg twice daily) (n=25). The pharmacist will randomize the groups at a 1:1 ratio of TAU:TAU and PEA. Subjects and researchers will be blinded to the study condition, but in the event that the blind needs to be broken, a randomization document will be locked in the pharmacy. The PI will determine if breaking the blind is necessary, and if so, the pharmacist will break the blind for the necessary subject(s).

Our study will provide insights on treatment strategies to prevent mood episodes and identify biomarkers able to monitor antidepressant response in BD. Our team includes Rodrigo Machado-Vieira and Jair C. Soares, both experts in Mood Disorders with large research experience, Dr. Lokesh Shahani, Medical Director of the UTHealth, Harris County Psychiatric Center, and well-trained Research Assistants from the Center of Excellence in Mood Disorders. This innovative approach indirectly targeting the cannabinoid system may shift the landscape of BD research by identifying a unique and therapeutically relevant target in BD.

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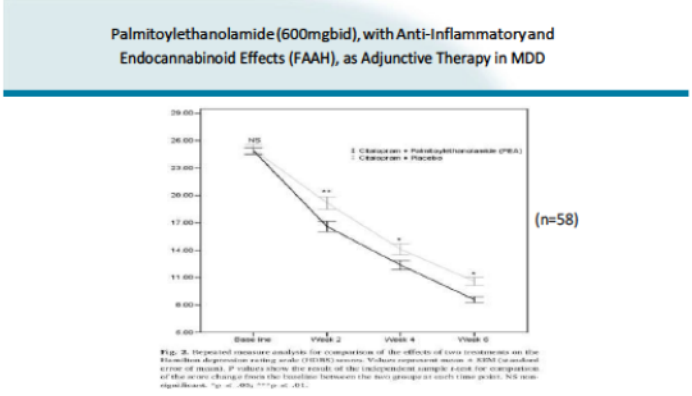
Overall Aim: To study the role of the endocannabinoid system (ECS) in the therapeutics of bipolar depression and evaluate the interaction between this system with EBs and inflammatory biomarkers.	**Timeline (Months)**	**UTHealth**
Major Task 1: Clinical Trial		
Subtask 1: IRB/HRPO/VA R&D regulatory approvals	1-3	X
Subtask 1: Treatment group 2: TAU plus PEA (600mg bid) (n=25) vs. TAU plus placebo (n=25) [6 weeks]	3-12	X
Major Task 2: Biomarkers		
Subtask 2: Endocannabinoid system (ECS) components in blood (RNA and protein levels) in bipolar depression (pre. vs post PEA) (n=25)	3-12	X

Target Enrollment (per quarter)	**Year 1**			
	Q1	**Q2**	**Q3**	**Q4**
UTHealth	5	15	15	15

Scientific approach

There are very few new FDA-approved agents for depressive episodes in bipolar disorder {BD). The endocannabinoid system (ECS) has a unique role in central nervous system {CNS) homeostasis and functions, such as neurotransmission, cell signaling, inflammation, as well as neuronal and glial cell proliferation, migration, and survival[1,2]. Endocannabinoids bind to CB1 receptors and affect the activity of monoamines (e.g., dopamine), excitatory {glutamate) and inhibitory {GABA, glycine) transmitters. Blunted ECS activity in Depression has been shown, while stimulation of the ECS induces antidepressant effects. Of special interest, chronic stress upregulates the key enzyme within the ECS, called fatty acid amide hydrolase {FAAH). FAAH is a classic endocannabinoid degrading enzyme located in the somatodendritic compartments of neurons and induces depression while pharmacological inhibition of FAAH promotes antidepressant effects[3]. Supporting this concept, genetic deletion and pharmacological inhibition of FAAH induce 10-15-fold higher brain levels of AEA[4]. FAAH is involved in the inactivation of the main EC anandamide {AE A)[5]. AEA has been shown to improve depressive-like symptoms by its indirect agonistic actions at the CB1 receptor[6]. Palmitoylethanolamide {PEA) is a nutraceutical proof of concept FAAH inhibitor. Palmitoylethanolamide (PEA) is produced in the body to limit pain and inflammation. PEA increases the main endocannabinoid anandamide (AEA) levels and activates the cannabinoid 1 (CB) receptor, the called entourage effect. PEA has shown to limit systemic inflammation by increasing AEA levels. Based on this inhibitory effect at FAAH breakdown, PEA limits the production of arachidonic acid, thus activating endocannabinoid signaling and limiting central and peripheral inflammation[7]. In neuroinflammation, a key mechanism present in depression, several clinical trials tested PEA with positive results and greater reductions of pain intensity {acute and chronic pain), migraine, and fi bromyalgia[7]. PEA also induces neurotrophic and antioxidant effects[8,9]. In the pilot double-blind, randomized and placebo-controlled trial with PEA in unipolar depression (600mg twice daily),



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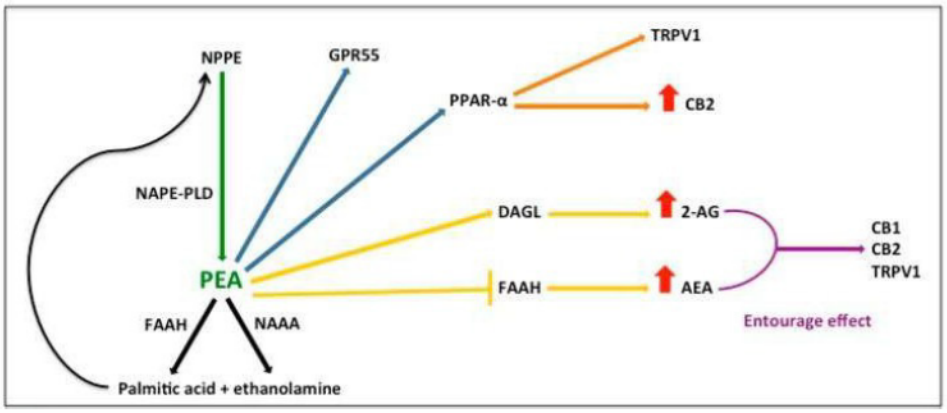
PEA adjunctive to citalopram showed superior antidepressant efficacy vs placebo after 6 weeks, with significant differences starting after 2 weeks (**Figure 1:** Ghazizadeh-Hashemi et al. Journal of Affective Disorders 232 (2018) 127-133). The group of patients receiving add-on PEA showed significantly greater improvement in HAM-D scores throughout the entire trial period {weeks 2, 4 and 6), in the absence of additional side effects. PEA revealed to be a safe and well-tolerated adjuvant to citalopram in patients with MDD. The PEA group showed rapid onset and significantly greater improvements in depressive symptoms score from week 2 compared to the placebo group. The observed Cohen's d was 0.82 while comparison of improvement in depressive scores at week 2 showed a large effect size for reduction of HAM-D scores in the PEA group compared to placebo[3]. Thus, PEA-induced increase in AEA levels and associated anti-inflammatory effects may represent a unique and promising therapeutic strategy in depression therapeutics. PEA is currently marketed as a nutraceutical. Ultra-micronized PEA (PEA-um) has shown high bioavailability and easily crosses the BBB, as demonstrated by the significant increase of PEA levels in the hippocampus after oral use of PEA -um10 after oral use. PEA-m and PEA -um have demonstrated positive safety profiles with no evidence of toxicity[11]. In the words of the Nobel Prize winner Rita Levi-Montalcini, "*The observed effects of PEA appear to reflect the consequences of supplying the tissue with a sufficient quantity of its physiological regulator of cellular homeostasis*" [7]. Importantly, unlike cannabis, FAAH inhibition does not produce reinforcing effects[9]. Overall, at present, there are no novel endocannabinoid-enhancer drugs on the market. PEA represents the only compound widely available able to safely boost the ECS and has demonstrated robust clinical effects in depression, pain and inflammatory conditions. We propose that the anti-inflammatory and ECS activating effects of PEA will bring about similar antidepressant effects in BD depression.



METHODS: This mechanistic, proof-of-concept study aims to investigate the antidepressant effects of the ECS agonist PEA. We aim to pharmacologically increase levels of PEA and evaluate longitudinal clinical and biological effects, including endogenous the key endocannabinoids AEA, 2-arachidonoylglycerol (2-AG) and oleoylethanolamide (OEA) (**Figure 2**). This 6-week, double-blind, placebo- controlled study aims to evaluate the antidepressant efficacy of the PEA in Bipolar Depression and the association between antidepressant response with endogenous cannabinoids and cytokines to evaluate the efficacy and obtain therapeutically relevant mechanistic insights. Results may support a role for the ECS as an alternative signaling pathway for drug development in BD. Description of Study Population: A total of 50 subjects with BD in a depressive episode (males and females) between ages 18-70 years old will be enrolled in the study. Study procedures, including consent, will take place at the Department of Psychiatry UTHealth, Houston or remotely via secure video-interface, if necessary. Both outpatients and inpatients from the behavioral sciences campus will be recruited to participate. In addition, patients with an active medical health records chart in EPIC who meet pre-screened eligibility and have indicated consent to contact on their chart will also be reached out to via email and telephone as an additional

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recruitment strategy. Only patients that are voluntarily checked in at the inpatient psychiatric facilities will be eligible to participate and may be treated while hospitalized, and will continue participation after discharge. Subjects with bipolar depression will be followed up for six weeks, with baseline and follow-up visits (weeks 2, 4 and 6). All participants will continue under TAU (mood stabilizers) and will be randomized to adjunctive PEA (600mg twice daily, n=25) or placebo (n=25). The primary outcome will be depression improvement (Hamilton Depression rating Scale, HAM-D) from baseline to week-6 versus placebo. Score change in HAM-D from baseline to endpoint compared between placebo versus active group is the primary outcome. All others (remission/response rates, and time to response or remission compared between PEA and placebo groups) are secondary outcomes. Also, additional outcomes include early improvement (first 2 weeks, >20% improvement from baseline), score changes (at each visit), response rates (defined as ≥50% reduction in the HAM-D score), remission rates (defined as HAM-D score Q) and time to response or remission will be also compared between PEA and placebo groups. The Montgomery-Äsberg Depression Rating Scale (MADRS) change from baseline to week six versus placebo will be used as a secondary outcome. Adverse events (on a side-effect checklist) will be evaluated at each time point along with vital sign (blood pressure, heartrate, temperature) and suicidality. Suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (CSSRS) at each visit. To inquire about adverse events and adverse events of special interest, non-leading and open ended questions will be used at each visit. Subjects will be withdrawn from the study due to significant adverse events (e.g. those causing extreme distress, significant impairment of functioning, and/or incapacitation preventing normal everyday activities), at the judgement of the PI and medical monitor. For safety purposes, the PI will be unblinded. Pregnant patients will be excluded from the study following a pre-randomization urine pregnancy test at the baseline visit. Adequate contraception methods for men and women of childbearing potential will be female birth control pills, intrauterine devices (IUD), injectable and male condoms, and abstinence. Subjects will be given a document detailing instructions for medication administration and a diary for drug accountability and side effect reporting. We will recruit participants seeking care for depression in BD or under current treatment at our large inpatient (UTHealth, Behavioral Sciences Campus) and our outpatient settings, the Behavioral and Biomedical Sciences Building (BBSB). There are potential direct potential benefits for the individual subject as a result of participating in the study. Those who respond to PEA will receive the medication for three additional months, if needed, under standard clinical care. PEA is expected to alleviate depression and other clinical dimensions, with no switch risk. Overall, we expect a highly favorable risk-benefit ratio for every subject involved in this study. At visit 1, research personnel will collect demographic information, including BMI (height/weight).

HYPOTHESES: Activation of ECS signaling has been postulated as a new promising pharmacological strategy to treat depression. We aim to evaluate the efficacy of PEA and detect evidence of a new therapeutic mechanism (inhibition of FAAH) to reduce depressive symptomatology in BD. **Primary Endpoint:** Evaluate the antidepressant effects of PEA in BD over the course of 6 weeks; Hypothesis 1: We hypothesize that the potentiation of eCB function with the FAAH inhibitor PEA will improve overall depressive symptomatology in BD compared to placebo. **Secondary Endpoint:** Evaluate whether the PEA-induced increase in AEA levels correlates with antidepressant effects over the course of 6 weeks; Hypothesis 2: Improvement of depressive symptoms correlates with a significant increase in AEA levels in the treatment.

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Schedule of Events

		Visit 1 (baseline)	Visit 2 (week 2)	Visit 3 (week 4)	Visit 4 (week 6, endpoint)
Efficacy Assessments					
	HAMD*	X	X	X	X
	MADRS*	X	X	X	X
	Blood Biomarkers*	X			X
	Randomization	X			
Safety Assessments					
	Physical Examination*	X			X
	Criteria Eligibility Review*	X			
	Vital signs*	X	X	X	X
	UDS (urine drug screen)*	X			
	Urine Pregnancy Test*	X			
	CSSRS*	X	X	X	X
	AE review	X	X	X	X

**Prior to randomization at baseline*

Inclusion Criteria: Eligible patients will be men and women aged 18-70 years with a diagnosis of Bipolar Disorder according to the Diagnostic and Statistical Manual of Mental Disorders (Structured Clinical Interview), Fifth Edition, (DSM5), with a score of ≥16 on the 17-item HAM-D; currently in use of at least one FDA approved mood stabilizer with or without antidepressant; medically and neurologically healthy on the basis of medical history, physical examination. Exclusion Criteria: Cannabis misuse according to clinical judgement; unstable medical condition or uncontrolled medical problem with known CNS effects; active DSM-5 substance use disorder in past three months (other than alcohol or nicotine use disorder); acute high suicidal risk; in a manic episode; current psychotic features or cognitive impairment that would preclude understanding of the consenting process or tests/examinations; pregnant or nursing women; unstable medical conditions; clinically significant abnormal laboratory tests based on complete blood count, liver and kidney function when available, pre-randomization.

GENERAL ANALYTIC STRATEGY: Analyses will rely on generalized linear modeling (GLM) with multilevel (GLMM) components to model outcomes using link functions for non-Gaussian outcomes and multilevel effects for correlated data (e.g., repeated measures). Analyses will rely on dual frequentist and Bayesian inference; the former evaluates the probability of the observed data, or data more extreme, given the null, while the latter directly yields the probability of an alternative hypothesis[12]. For Bayesian analyses,

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weakly informative priors (e.g., b~N[μ=0,σ2=10]) will maximize the influence of the data on posterior probabilities (PP). Sensitivity analyses will evaluate robustness to prior specifications[13]. Residual plots, effective sample size, scale reduction factors, and posterior predictive checking will assess assumptions; violations will be addressed by transformation or respecification. Primary analyses will evaluate an intent-to-treat sample; complementary follow-up analyses will evaluate a per protocol sample. Models will handle missingness via maximum likelihood, explicit modeling of missingness[14], and/or imputation with sensitivity analyses to evaluate the robustness of findings. Bayesian analyses are less influenced by multiple comparisons due to calibrating probability via the prior and the Likelihood Principle[15]; however, additional analyses will employ regularized priors[16,17] to maximize the robustness of effects. Frequentist analyses will evaluate any post hoc tests with false discovery rate Type I error correction. Bayesian evidence will be characterized by PP threshold guidelines18 as moderate (PP=75%-90%), strong (PP=91%-96%), and very strong (PP 97%). A threshold PP 75% will be considered a minimum degree of evidence in favor of committing further resources to investigating the treatment. Preliminary analyses will inspect relationships between sample characteristics and study predictors/outcomes. Characteristics related to both predictor and outcome variables may be confounders[19, 20]; models with and without covariate adjustment will be reported if inferences are different. Models will adjust for intractable covariates (sex; age) and the stratification variable (baseline depression severity). Follow-up models will evaluate differences across sexes and other potential moderators. Analyses will be performed in R[21] via packages lme4[22], rstan, and brms[23]. (**SPECIFIC ANALYSES:** All analyses will include any potential confounds or essential covariates (identified by criteria above) and a random effect structure that best fits the data (i.e., random intercept/slope/both). Aim 1- Hypothesis 1. The potentiation of eCB function with the FAAH inhibitor PEA will improve overall depressive symptomatology in BD compared to placebo. GLMM will model dichotomous response to treatment at the end of the trial (yes vs. no; 50% reduction in HAM-D) as a function of treatment group. To evaluate temporal change, follow-up analyses will use GLMM to model raw HAM-D scores as a function of the interaction between treatment and time, controlling for all constituent lower-order main effects. Aim 2 - Hypothesis 2. Improvement of depressive symptoms correlates with a significant increase in AEA levels in the treatment group. GLMM will model temporal change in depressive symptoms as a function of time and AEA levels, where the time-varying nature of AEA levels is handled via decomposing the effect into multiple variables to accurately account for between- and within-person variation[24].

POWER AND EFFECT SIZE: Considerations for the current proposal focus on detecting an effect of PEA on bipolar depression response rate (50% reduction in HAM-D) at the end of treatment and calculated via G*Power from the frequentist perspective. Assuming (1) a sample size N = 50 (25/group) and (2) a 39.2% response rate for placebo[25] (X), the proposed trial has 80% power to detect a 77.4% response rate for PEA. This difference in response rates is equivalent to a large OR= 5.31. The feasibility of this effect size is supported by the closest available comparators in the literature, supporting large effects of 600 mg PEA on unipolar depression (Cohen's D = 0.82; 3 and lumbosciatica (Cohen's D = 1.35;[26]).

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