Systematic Review

Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis

Bekir Berker Artukoglu, MD[1], Chad Beyer, MBChB[1], Adi Zuloff-Shani, PhD[2], Ephraim Brener, PhD[2], and Michael Howard Bloch, MD[1]

From: [1]Yale Child Study Center, New Haven, CT; [2]Therapix Biosciences, Tel Aviv, Israel

Address Correspondence:
Bekir Berker Artukoglu, MD
Yale Child Study Center
Bloch Lab,
Nieson Irving Harris Building
230 S. Frontage Rd, Ste I-375
New Haven, CT 06519
E-mail:
artukoglubekir@gmail.com

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Background: Palmitoylethanolamide (PEA) is a cannabimimetic compound that has been investigated as an analgesic agent in animal models and clinical trials.

Objectives: We conducted a meta-analysis to examine the efficacy of PEA for treating pain in randomized, controlled trials.

Study Design: Systematic review and meta-analysis.

Setting: This meta-analysis examined all randomized, controlled trials involving the effect of PEA on pain score.

Methods: We searched PubMed and Embase for randomized, active or placebo-controlled trials of PEA for the treatment of acute or chronic pain. Our primary outcome was the weighted mean difference in visual analog pain scales of PEA treatment compared to inactive controls.

Results: We identified 10 studies including data from 786 patients who received PEA and 512 controls for inclusion in our systematic review. Eight trials included an inactive control group and were included in the meta-analysis. PEA was associated with significantly greater pain reduction compared to inactive control conditions (WMD = 2.03, 95% CI: 1.19 – 2.87, z = 4.75, $P < 0.001$). Use of placebo control, presence of blinding, allowance for concomitant treatments, and duration or dose of PEA treatment did not affect the measured efficacy of PEA. All-cause dropout was non-significantly reduced in the PEA group compared to inactive control conditions (RR = 0.36, 95% CI: 0.10 – 1.26, z = -1.60, $P = 0.11$).

Limitations: This meta-analysis relied on a relatively small number of trials across a variety of conditions causing pain with differing trial designs. Overall quality of the underlying studies and assessment of side effects were often poor.

Conclusions: PEA may be a useful treatment for pain and is generally well tolerated in research populations. Further, well-designed, randomized, placebo-controlled trials are needed to provide reliable estimates of its efficacy and to identify less serious adverse events associated with this compound.

Key words: PEA, palmidrol, palmitoylethanolamide, efficacy, pain, pain management, meta-analysis

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Chronic pain is estimated to affect 43% of the US population and 38% of people worldwide, over a 12-month period (1). According to an analysis of the World Health Organization's Global Burden of Health 2010 study, 5 of the top 10 conditions responsible for the most Years Lived with Disability (YLD) globally were characterized by the presence of different kinds of pain such as low back pain, headache, and dental pain (2). The economic burden of pain in the United States is estimated at $650 billion per year in

health care (3), and the citizens face a reduced quality of life as well as lost economic productivity.

Several medications exist that are effective at reducing pain but are associated with a substantial side-effect burden to varying degrees. Opiate medications, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antidepressants, and anticonvulsants are all currently utilized to treat chronic and/or acute pain (4). Opiates are commonly used for the management of acute pain but evidence of their efficacy and risk-benefit profile in treating chronic pain is not as robust (5,6). Use of opiate medications to treat pain is associated with significant side-effects including constipation, respiratory depression, impaired cognitive ability, immune suppression, and opioid-related endocrinopathies (7). Chronic use of opiate medications is associated with the development of tolerance and dependence (7). The risk of diversion and overdose with opiate medications is also a significant burden to society and individuals when these medications are misused or abused. The primary medications used to manage chronic pain in the US are NSAIDS such as aspirin and they are especially effective when pain is of an inflammatory origin. NSAIDs are safe when used in patients who are not at high risk for gastrointestinal, renal, or cardiovascular reactions (8). Newer selective NSAIDs, such as celecoxib, selectively inhibit cyclooxygenase-2 (COX-2) which is responsible for synthesizing the pro-inflammatory prostaglandins (9). Large randomized controlled trials have demonstrated that use of COX-2-selective NSAIDs are associated with a reduced risk of NSAID ulcers and gastrointestinal complications (10,11), although their use is associated with an increased risk of myocardial infarction (12).The addition of an NSAID to a pain management regimen for treating acute pain can have an opioid-sparing effect by reducing the consumption of supplementary opioids (13,14). This is of public health significance considering that opioid analgesics were involved in 43% of all drug overdose deaths in the USA in 2010 (15). Acetaminophen is another non-opiate oral analgesic that, according to meta-analysis that used pain scales, is less effective in pain management than NSAIDs with a similar rate of adverse events (16,17). It may not bring clinically significant improvement in certain types of chronic pain such as low-back pain and osteoarthritis (18). Its use within therapeutic limits is associated with aminotransferase elevations (19) and acetaminophen overdose commonly leads to hepatotoxicity making it one of the leading causes of drug toxicity and suicide (20). Use of tricyclic antidepressants for pain management has been well-established over the years (6) but a recent systematic review suggests an overestimation of treatment effect (21). Some of the side effects associated with this class are postural hypotension, dry mouth, and sedation in the elderly population which leads to an increased risk for falls and fractures (4).

Cannabinoids, chemical compounds that are produced naturally in the body and may also be found in plants belonging to the genus Cannabis, act on cannabinoid (CB) receptors in the central nervous system (CNS) and cells of the immune system (22). Currently available drug trials and meta-analyses appear to support the use of cannabinoids for the treatment of chronic pain (23,24). High concentrations of CB1 receptors on primary afferent nociceptors in the dorsal spinal cord may explain the anti-nociceptive effects of cannabis (25). The effects of endocannabinoids on the peripheral CB2 receptors of the immune system suggest that they may also be effective for treating inflammatory pain (26). Cannabis-related compounds commonly have short-term adverse effects such as asthenia, confusion, somnolence, balance problems, and gastrointestinal side effects (23,24). There is also evidence that cannabis use increases the risk of psychotic outcomes independently of confounding and transient intoxication effects (27). Additionally, the use of many cannabis-related drugs is tightly regulated and restricted.

Palmitoylethanolamide (PEA) is a cannabimimetic compound and lipid messenger hypothesized to reduce pain through (1) a variety of endocannabinoid driven activities that were discussed earlier or (2) reducing inflammation. PEA does not bind the classical cannabinoid receptors but may indirectly stimulate the effects of both phyto- or endocannabinoids, either by its role as an agonist of the transient receptor potential vanilloid type 1 (TRPV1), peroxisome proliferator-activated receptor-α (PPAR-α) and the cannabinoid receptors (28). Many clinical trials and studies using animal models (29) have been conducted to assess the clinical relevance of PEA as a stand-alone analgesic agent or as a part of combinational therapy. PEA's analgesic actions may be due to its agonism of peroxisome proliferator-activated receptor-α (PPAR-α) which has been shown to have a pivotal role in the PEA pharmacodynamic mechanisms for pain relief (30). PEA plays an important role in suppression of inflammation by reducing the activity of the pro-inflammatory enzymes such as COX, eNOS, and iNOS (31) and by reducing mast cell activation (30,32,33). PEA reduces mast cell migration,

degranulation, and over-activation of astrocytes and glial cells (34-37).

Several controlled clinical trials have been conducted over recent years to examine the efficacy of PEA in treating chronic pain associated with a variety of conditions. With this meta-analysis using randomized controlled trials, we aim to examine the efficacy of PEA for treating chronic pain. With the use of previous randomized controlled trials, we will also examine the tolerability of PEA.

Methods

Search Strategy for Identification of Studies

Two reviewers (BA, CB) searched the electronic databases of PubMed and Embase on May 1, 2015, for relevant studies using the search: ([Cannabis OR cannabinoid] OR [Palmitoylethanolamide OR palmidrol] AND [chronic pain OR inflammatory pain OR acute pain OR intractable pain OR postoperative pain OR neuropathic pain) AND (pain assessment OR pain intensity OR pain severity]).

They restricted the search to randomized controlled trials. The references of appropriate papers and previous reviews were searched for citations of further relevant published and unpublished research (38).

Selection of Studies

The titles and abstracts of studies obtained by this search strategy were examined by 2 reviewers (BA, CB) to determine inclusion in this meta-analysis. Any discrepancies were resolved by a final reviewer (MHB). Eligibility for the study was based upon analysis of the full articles for the following criteria: they needed to (1) be randomized, (2) placebo or comparator controlled clinical trials looking at the use of PEA (3) to treat or alleviate acute or chronic pain, brought about by conditions with explicit criteria such as those found in the International Classification of Diseases (ICD). Discontinuation studies or studies which involved duplication of data from prior reported research included in this review were excluded. Head-to-head studies without a placebo control and crossover trials were not excluded. Studies requiring concomitant medications were not excluded. We additionally restricted trials to treatment trials, as studies using non–treatment-related outcome measures such as magnetic resonance imaging (MRI), electroencephalography (EEG), or neuropsychological testing were less likely to systematically assess side effects of medications.

Meta-Analytic Procedures

Data were extracted by independent reviewers (BA, CB) on specially designed Microsoft Excel spreadsheets. Our primary outcome measure was the efficacy of PEA for the management of chronic pain across a wide range of conditions. The visual analog scale (VAS) was used to gather subjective pain sensation. Reviewers also gathered data on patients' conditions, trial design, maximum daily PEA dose, number of participants in active group, number of participants in placebo group, concomitant treatment in active and control group, and other relevant attributes and results of the studies. Any disagreement among reviewers was mitigated through discussion and the procurement of more information from the study investigators if possible. When agreement could not be attained between the initial reviewers, the senior investigator (MHB) resolved all disputes. When information about the efficacy of PEA for the management of chronic pain was not available in the original manuscripts, the corresponding author was contacted for further information. If contacting the corresponding author was ineffective, we also searched pharmaceutical company databases for the data.

All statistical analyses were completed in Comprehensive Meta-Analysis Version 3 (39). For our outcome measures of interest, the efficacy of PEA for the management of chronic pain was analyzed using mean difference in endpoint VAS scores on a 1 – 10 scale for PEA versus control conditions. A random-effects model was used as the primary method for meta-analysis as it is more conservative but results from a fixed-effects model is presented in sensitivity analysis. Publication bias was assessed by plotting the effect size against standard error for each included trial (i.e., funnel plot). In addition, publication bias was statistically tested by the Egger test and by determining the association between sample size and effect size in meta-regression.

For our primary analysis, we grouped trials by PEA dose, duration of treatment, and trial characteristics (blinding and control condition). We examined the following questions in meta-analysis: (1) is PEA effective for treating pain; (2) is dosing of PEA associated with an increased efficacy; (3) is the duration of dosing of PEA associated with an increased efficacy; and (4) do trial characteristics (blinding and control condition) have an association with the efficacy of PEA.

All subgroup analyses were performed using a fixed-effects model to conduct a test for subgroup differences (between-group heterogeneity χ^2). Meta-

regression analysis was used to examine the effects of maximum daily dose of PEA used in trials. Our threshold for statistical significance was $P < 0.05$ for the primary analysis, as well as for all stratified subgroup analyses and meta-regression.

Results

Included Trials

Figure 1 depicts the selection of trials for this meta-analysis. A total of 25 references were identified in PubMed and Embase. A total 10 randomized clinical tri-

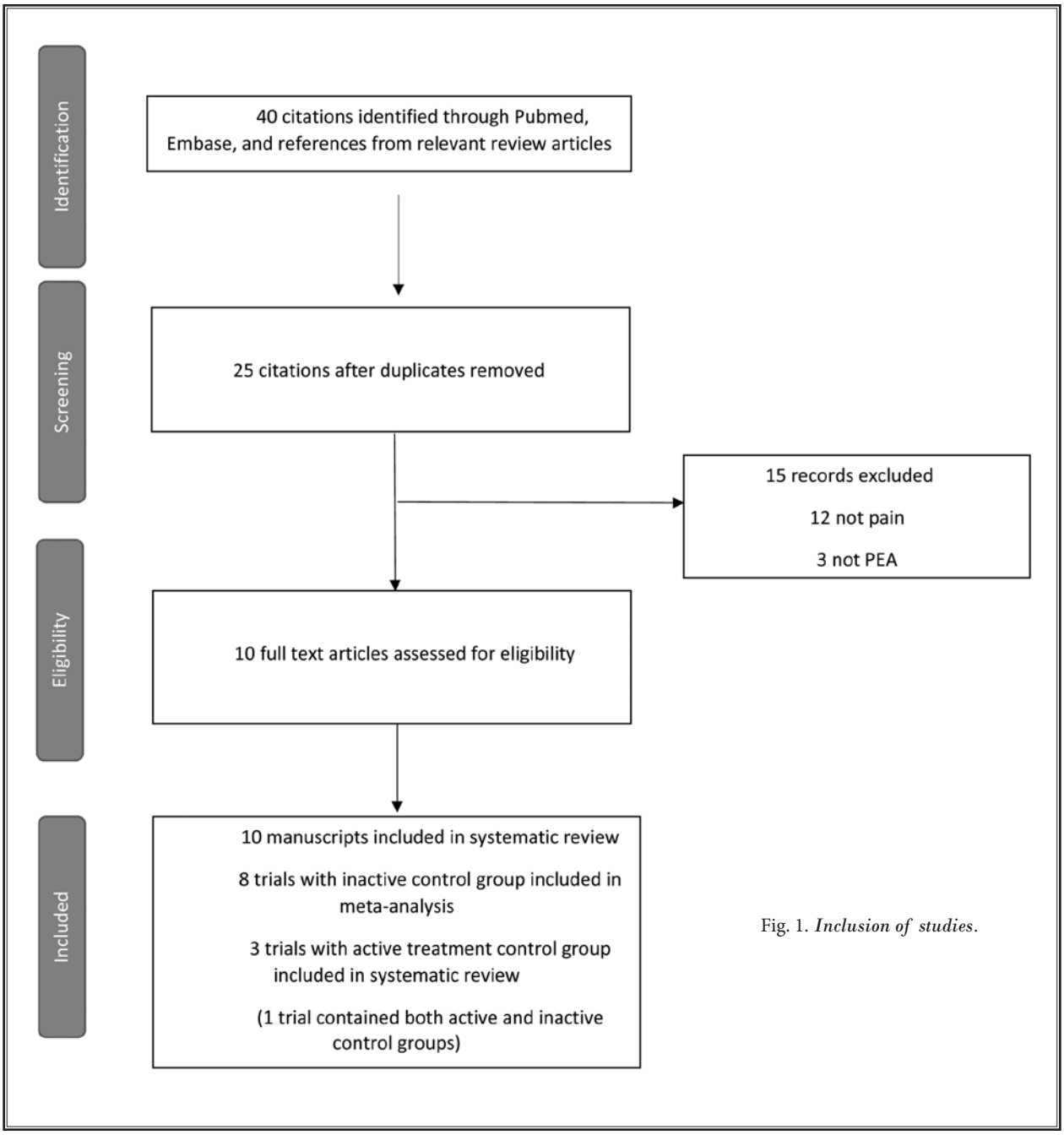

Fig. 1. *Inclusion of studies.*

als were eligible for potential inclusion once the titles, abstracts, and full texts (where necessary) were reviewed (40-49).These trials included data from 786 patients who received PEA and 512 controls. Eight of these studies were randomized controlled trials with 743 patients receiving PEA and 460 patients receiving inactive controls (placebo [trials = 5, patients = 37]) or no treatment [trials = 3, patients = 90]). One trial contained both active and inactive control groups (43). The characteristics of included trials are presented in Table 1.

PEA versus Inactive Control Conditions

Efficacy

Figure 2 depicts the effect of PEA on pain compared to inactive control conditions in randomized controlled trials. PEA was associated with significantly greater pain reduction compared to inactive control conditions (WMD = 2.03, 95% CI: 1.19 – 2.87, z = 4.75, $P < 0.001$). There was significant evidence of heterogeneity between trials (χ^2 test for heterogeneity = 65.1, df = 7, $P < 0.001$, $I^2 = 89\%$). There was some asymmetry in the funnel plot of included trials suggesting possible publication bias. However, the Egger's test did not reach statistical significance given the small number of trials ($P = 0.83$). A fixed-effects model also reported a significant benefit of PEA compared to control conditions (WMD = 2.20, 95% CI: 2.00 – 2.41, z = 21.4, $P < 0.001$).

Stratified subgroup analysis did not demonstrate a significant association between aspects of trial design – use of placebo-control (test for subgroup differences $\chi^2 = 2.47$, df = 1, $P = 0.12$) or blinding (test for subgroup differences $\chi^2 = 1.18$, df = 1, $P = 0.28$) and measured efficacy

Table 1. *Study characteristics.*

Study, Year	Indication	PEA Dose (mg/day)	Duration (days)	Active group – Adj treatment	Control	Active:Control	NSAIDS	Blinded
Inactive Control Group								
Bacci et al, 2011	Molar Surgery	600	15	None	No Placebo	26:26	No	No
Canteri et al, 2010	Sciatic pain	300;600	21	None	Placebo	76:22	No	Yes
Cobellis et al, 2011	Chronic pelvic pain	800	90	Polydatin 80 mg	Placebo	21:20	No	Yes
Conigliaro et al, 2011	Carpal Tunnel Syndrome	600;1200	30	None	No Placebo	14:12	No	No
Domínguez et al, 2012	Sciatic pain	600	30	None	No Placebo	62:52	No	No
Guida et al, 2010	Sciatic pain	300;600	21	None	Placebo	424:208	No	No
Murina et al, 2013	Vestibulodynia	800	60	Transpolydatin 80 mg	Placebo	10:10	No	Yes
Tartaglia et al, 2015	Pelvic Pain	400	10	Transpolydatin 40 mg	Placebo	110:110	No	Yes
Active Control Group								
Cobellis et al, 2011	Chronic pelvic pain	800	90	Polydatin 80 mg	Celecoxib 200 mg BID for 7 days	21:20	Yes	Yes
Marini et al, 2012	TMJ arthritis	900	14	none	Ibuprofen 600 mg TID for 2 weeks	12:12	Yes	Yes
Di Francesco et al, 2014	Chronic Pelvic Pain	800	180	Transpolydatin 80 mg	Leuprorelin acetate (11.25 mg/2 mL) one vial every 3 months in 180 days Ethinylestradiol+Drospirenone (0.03 mg+3 mg) p.o for 180 days	10:10:10	No	No

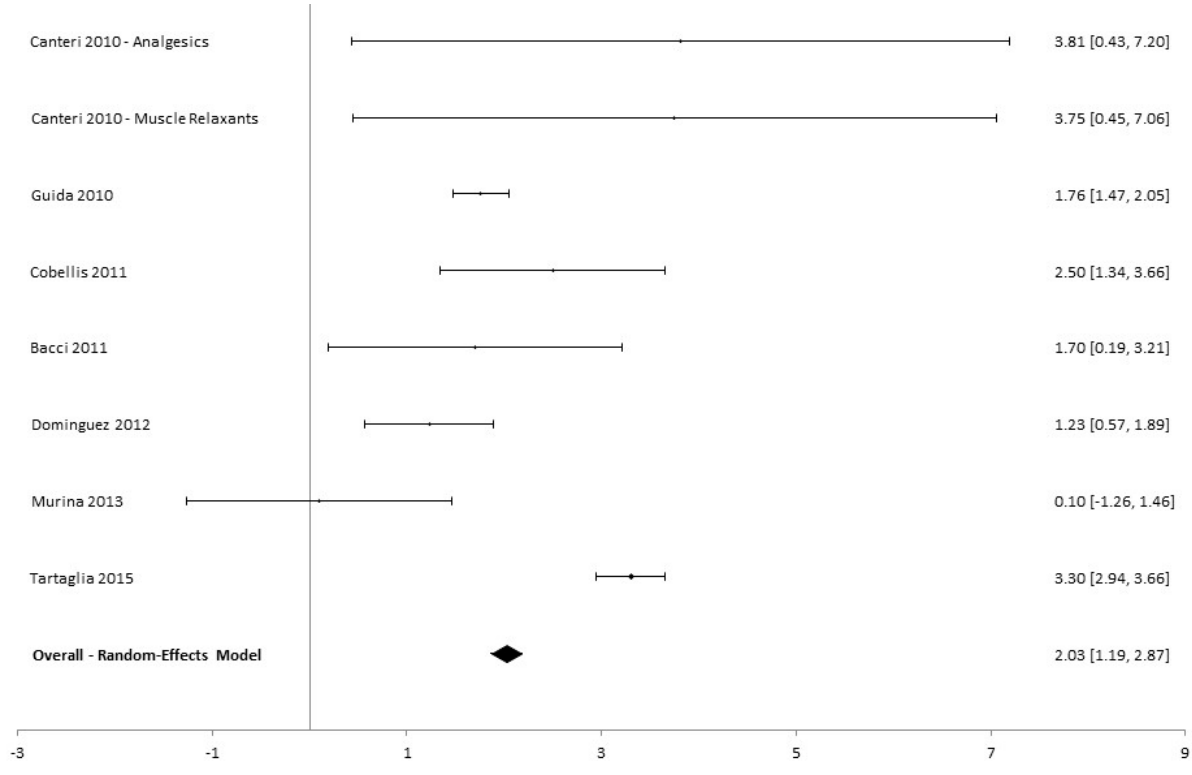

Fig. 2. *Forest plot*.

of PEA. Trials that were blinded (WMD = 2.46, 95% CI: 1.05 – 3.86, z = 3.43, $P < 0.005$, k = 5) demonstrated similar effects of PEA compared to non-blinded trials (WMD = 1.66, 95% CI: 1.38 – 1.95, z = 11.4, $P < 0.005$, k = 3). Trials that were placebo-controlled (WMD = 2.27, 95% CI: 1.23 – 3.31, z = 4.27, $P < 0.005$, k = 6) demonstrated similar measured efficacy of PEA compared to trials that did not include placebo (WMD = 1.31, 95% CI: 0.70 – 1.91, z = 4.25, $P < 0.005$, k = 2). There was also no difference in measured efficacy of PEA based on whether additional treatments/additives were employed in the active arm (test for subgroup differences $\chi^2 = 0.18$, df = 1, $P = 0.67$) or across both active and control conditions (test for subgroup differences $\chi^2 = 0.03$, df = 1, $P = 0.85$).

The daily dosage of PEA ranged from 300 mg to 1200 mg and a majority (n = 8) of the studies used PEA doses of 600 mg/d or greater (600 – 1200 mg/d), but a meta-regression demonstrated no significant association between dose of PEA and measured efficacy (parameter estimate (PE) = -0.0010, 95% CI: -0.0042 – 0.0023, z = -0.58, $P = 0.56$). Likewise, although the duration of treatment ranged from 10 to 180 days, a meta-regression failed to show a significant association between increased duration of treatment and pain efficacy (PE = -0.012, 95% CI: -0.042 – 0.019, z = -0.76, $P = 0.45$).

Tolerability

Meta-analysis suggested that all-cause dropout was reduced but not to a significant degree in the PEA group compared to inactive control conditions (RR = 0.36, 95% CI: 0.10 – 1.26, z = -1.60, $P = 0.11$). The all-cause dropout rate was 1.1% with PEA treatment (14 out of 1,269 patients) compared to 4.3% (32 out of 738 patients) in the inactive control groups. Adverse events reported with PEA treatment in previous trials included gastrointestinal upset (2), drowsiness (1), and heart palpitations (1).

PEA versus Active Control Conditions

Three trials have examined the efficacy of PEA compared to various active control conditions. A randomized controlled trial compared the efficacy of PEA

plus trans-polydatin to (a) leuprorelin acetate or (b) ethinylestradiol and drospirenone in 30 patients with chronic pelvic pain over a 6-month treatment course. All 3 treatments resulted in a significant reduction in pain over the course of the trial (PEA and trans-polydatin [$P = 0.0004$], leuprorelin acetate [$P < 0.0001$] and ethinylestradiol and drospirenone [$P = 0.04$]). However, specific type of treatment was not significantly associated with the degree of pain reduction (47). No adverse effects were detected in any of the groups in the course of the study.

A triple blinded randomized controlled trial compared the efficacy of PEA to ibuprofen in 24 patients with temporomandibular joint arthritis (TMJ) arthritis over a 2-week period. PEA was associated with a significantly greater pain reduction compared to ibuprofen ($P = 0.0001$). Three patients in the ibuprofen group reported stomach ache as an adverse event whereas PEA patients did not report any adverse events (41).

A double blind, randomized controlled trial compared the efficacy of PEA and transpolydatin to celecoxib (200 mg twice a day for 7 consecutive days) and placebo for 61 patients with chronic pelvic pain due to endometriosis over a 3-month period. Both treatment groups were more effective than placebo ($P < 0.001$) but the 2 active treatments did not differ significantly in terms of pain reduction. None of the groups reported significant adverse events (43).

Discussion

This meta-analysis provides preliminary evidence that PEA may be effective in the management of chronic pain across a variety of conditions. However, there was a large amount of heterogeneity between trials indicating that PEA may have differing efficacy (or measured efficacy) across conditions and/or trial designs. Despite examining several potential causes of heterogeneity, we were not able to demonstrate a likely cause – PEA dose, duration of treatment, and trial characteristics (blinding and control condition) were not significantly associated with measured efficacy of PEA. Additionally, in the existing PEA trials for pain, PEA was quite well tolerated with a reduced dropout rate compared to control conditions and no specific adverse events reported at a higher rate than control conditions.

Given the potential clinical importance of the meta-analysis, it is important to highlight the existing limitations. This meta-analysis relied on a relatively small number of trials with differing trial designs across a variety of conditions causing pain. Therefore, it is not surprising that the included trials differed significantly in their estimates of the underlying benefits of PEA. These underlying differences in sample populations and trial design likely caused the significant heterogeneity observed in this meta-analysis. We had limited power in this meta-analysis to examine sources of heterogeneity given the small number of trials. Additionally, although this meta-analysis was restricted to randomized trials, the overall quality of the underlying studies was often poor. Specifically, many included trials were not blinded or had unclear blinding of PEA and/or lacked a placebo control. These limitations could positively bias the measured efficacy of PEA and influence dropout estimates, even if we were unable to demonstrate this in our analysis. Few of the studies reported and controlled for concomitant treatments that pain patients were using before or during the trials. If trials failed to monitor and control for these treatments it may cause the measured benefits of PEA to be understated. Lastly, although dropout rates were reliably reported across studies, the small rate of adverse events across treatment arms suggests that side effects were not systematically assessed across trials. Although, serious adverse events were reported across trials, adverse effects of less severity are not reported. This methodology may not allow us to detect common, less severe experiences of patients taking PEA that may ultimately decrease PEA's tolerability.

Given the limitations of the underlying trials in the meta-analysis, we would suggest the following improvements for future research in this area: (1) use randomized, placebo-controlled research methodology even if the resultant trial will be underpowered so that unbiased measurements of efficacy and tolerability can be obtained; (2) conduct and report systematic measurement of adverse events in both the PEA and control groups; (3) conduct dose-finding studies which directly compare different doses of PEA such that an optimal dose of PEA can be established; (4) design trials to assess the short-term and more chronic effects of PEA treatment even if PEA is being used to treat chronic conditions so that we can have more reliable estimates of PEA's effects on acute pain; and (5) control and report use of concomitant treatments utilized by patients in trials.

This meta-analysis provides preliminary evidence that PEA may be a useful treatment for pain and is generally well tolerated in research populations. However, there was a large amount of heterogeneity in

the measured efficacy of PEA across conditions and several included trials were of poor overall quality. PEA represents a potentially promising treatment for pain that may offer several advantages over currently available treatments. Further, well-designed, randomized, placebo-controlled trials are needed to establish the efficacy of PEA and also to provide reliable estimates of less serious adverse events associated with this compound.

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Bekir B. Artukoglu had access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Bekir B. Artukoglu and Chad Beyer managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Drs Adi Zuloff-Shani, Ephraim Brener and Michael H. Bloch provided revision for intellectual content and final approval of the manuscript.

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