CNS & Neurological Disorders - Drug Targets, 2019, *18*, 491-495

POST HOC ANALYSIS OF A CLINICAL TRIAL

Micronized Palmitoylethanolamide: A Post Hoc Analysis of a Controlled Study in Patients with Low Back Pain – Sciatica

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Abstract: ***Background*:** Despite being widely prescribed, relatively few controlled trials have been conducted on the class of neurotrophic/antinociceptive nutraceuticals. While performing a search in the literature, we came across an old registration study on micronized palmitoylethanolamide in patients with low back pain – sciatica by Guida and colleagues.

***Methods*:** We contacted the authors of the article and obtained all the original material, which allowed us to reanalyze the study. We assessed its clinical relevance by calculating the numbers needed to treat for pain (visual analog scale) and function (Roland-Morris Questionnaire). After excluding patients for whom the information available was insufficient, we assigned each patient to one of the five categories of increasing probability of neuropathic pain: pure lumbago, lumbago with projecting pain to surrounding regions (*e.g.* gluteus or groin), lumbago with projecting pain to the thigh or leg, pure sciatica and radiculopathy, and investigated any correlations (Spearman) between the improvement in pain and function with these five classes.

***Results*:** Compared with placebo, palmitoylethanolamide 600 mg/die yielded a number needed to treat of 1.7 (95% confidence interval: 1.4-2) for pain, and 1.5 (95% confidence interval: 1.4-1.7) for function. The correlation between the five categories was highly significant for pain relief (P <0.0001), though not significant for reduced dysfunction.

***Conclusion*:** Palmitoylethanolamide was extremely effective on pain and function in a large cohort of patients with low back pain – sciatica. Although, the multiple mechanisms of action of palmitoylethanolamide are ideal for mixed pain conditions such as low back pain – sciatica, the correlation between pain relief and the likelihood of neuropathic pain suggests that this drug exerts a predominant action on the neuropathic pain component.

ARTICLE HISTORY

Received: January 15, 2019
Revised: May 20, 2019
Accepted: June 18, 2019

DOI:
10.2174/1871527318666190703110036

Keywords: Micronized palmitoylethanolamide, low back pain, neuropathic pain, mixed pain, nutraceuticals, NSAIDs, placebo.

1. INTRODUCTION

Some nutraceuticals considered to be effective in neuroprotection and pain, such as alpha-lipoic acid, acetyl-L-carnitine, and Palmitoylethanolamide (PEA), are supported by a large body of literature [1-7] though not by controlled trials, which are very limited in number.

Low back pain is a very common condition that causes marked disability and is a considerable socioeconomic burden [8, 9]. Up to 70% of people will experience low back pain during their lifetime [10]. Commonly used pharmacological agents include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioid analgesics, though both these classes of drugs have safety problems related to chronic treatment [11]. Despite the need for alternative treatment options with a better safety profile, the body of data available in the literature is still scanty [12]. We came across a registration study on micronized PEA (particle size range 0.5-10 μm) conducted by Guida and colleagues on a large cohort of patients with low back pain – sciatica [13], *i.e.* a condition of mixed nociceptive and neuropathic pain [14, 15]. This article had previously almost completely been ignored because the journal in which it had been published was not indexed by the main medical databases. We contacted the authors of the article and obtained all the original material, which allowed us to reanalyze the data and assess the clinical impact of the drug as well as its efficacy in neuropathic *vs*. nociceptive pain.

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1996-3181/19 $58.00+.00

2. METHODS

2.1. Original Study

Guida *et al.* (2010) [13] conducted a multicenter, double-blind, placebo-controlled, three-week, three-arm randomized study on 636 patients (53% males and 47% females) with "lumbosciatic algias". The two active arms were treated with micronized PEA (particle size range 0.5-10 μm) 300 mg and 600 mg per day. The inclusion criteria were lumbosciatalgia caused by truncal and/or radicular compression of the sciatic nerve or discopathy, both of which were diagnosed *via* an exhaustive clinical exam (and additional diagnostic tests, as required).

The authors measured pain using the Visual Analog Scale (VAS) and dysfunction using the Rolan-Morris Disability Questionnaire (RMDQ) [16]. The results were reported as means ± SDs and the statistical significance was assessed using ANOVA for comparisons between the three groups and the Scheffé test for comparisons between two groups.

2.2. The Number Needed to Treat and to Harm

We calculated the percentage of patients in whom at least 50% pain relief and at least 50% improvement in the RMDQ was achieved in each of the three groups of patients and then calculated the Numbers Needed to Treat (NNT) versus placebo using the standard method [17].

To calculate the Numbers Needed to Harm (NNH), we determined how many patients discontinued treatment because of adverse events compared with those who completed the study.

2.3. Correlation between Efficacy and Probability of Neuropathic Pain

We assigned patients to one of the following five categories of increasing probability of neuropathic pain: (1) pure lumbago, (2) lumbago with projecting pain to surrounding regions (*e.g.* gluteus or groin), (3) lumbago with projecting pain to the thigh or leg, (4) pure sciatica and (5) radiculopathy. Two of us, who were blinded to the treatment efficacy in the individual patient, independently selected the category on the basis of the description of the painful territories, the neurological examination and the imaging or neurophysiological data when available. Nineteen out of 619 patients were assigned to different categories by the two examiners while 22 had insufficient or contradictory information. Hence 41 patients (6.6 %) were excluded from the analysis. The correlation between pain and function improvement and the pain category was assessed by using a non-parametric test (Spearman's R correlation coefficient).

3. RESULTS

3.1. Original Study

Seventeen patients dropped out: 12 in the placebo, two in the 300-mg and one in the 600-mg groups. The study revealed a positive effect both on pain and functional measures ($P < 0.001$), with the 300-mg group, yielding a better effect than placebo and the 600-mg group, yielding a better effect than either the placebo or the 300-mg group.

3.2. NNT and NNH

NNT Results are shown in Table **1**. NNHs were not significant for either group.

3.3. Correlation between Efficacy and Probability of Neuropathic Pain

We found a significant correlation between pain category and pain relief, *i.e.* the higher the probability of suffering from neuropathic pain, the better the treatment outcome (Fig. **1**). By contrast, no significant correlation emerged between pain category and functional improvement.

4. DISCUSSION

The study by Guida *et al.* (2010) [13], who enrolled more than 600 patients with low back pain and various degrees of radicular pain, is probably the largest controlled, randomized trial designed to assess the effect of micronized PEA on pain and function to date. Low back pain is regarded as a mixed pain [15, 17] owing to the difficulties involved in disentangling its nociceptive and neuropathic components. We reanalyzed the data from Guida *et al.*'s study [13] in order to assess the clinical importance of PEA treatment and understand whether PEA is similarly effective on the nociceptive and neuropathic components of pain.

PEA is a naturally occurring endogenous fatty acid amide of palmitic acid and ethanolamine and a congener of the endocannabinoid anandamide that is endowed with anti-inflammatory and anti-hyperalgesic properties involved

Table 1. NNT. A: Active 300 mg. B: Active 600 mg. Res: Responders. Non-R: Non-Responders. CI: 95% Confidence Intervals. p: Fisher's Exact Test. RMDQ: Roland Morris Disability Questionnaire.

Visual Analog Scale	Placebo	PEA 300 mg	PEA 600 mg	NNT Placebo-PEA 300 mg	NNT Placebo-PEA 600 mg
≥50% Pain relief	Res: 46 Non-R: 163	Res: 70 Non-R: 142	Res: 176 Non-R: 39	9 (CI: 5-29) P<0.02	1.7 (CI: 1.4-2) P<0.0001
RMDQ Total score	-	-	-	-	-
≥50% improvement	Res: 47 Non-R: 162	Res: 81 Non-R: 131	Res: 189 Non-R: 26	6.4 (CI: 4-14) p <0.005	1.5 (CI: 1.4-1.7) p <0.0001

in a wide range of biological systems and pathological conditions [18-20].

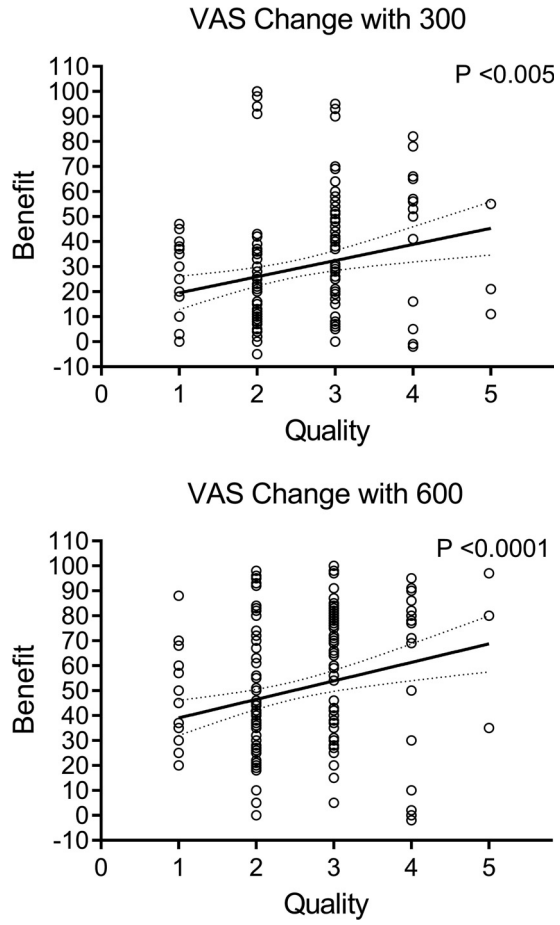

Fig. (1). Correlation between efficacy and probability of neuropathic pain. Y-axis: % change in VAS from baseline to end of study. X-axis: each patient (represented by a circle) was assigned to one of five categories of increasing probability of neuropathic pain: 1, pure low back pain. 2, low back pain with pain projecting to surrounding regions (*e.g*. gluteus, groin). 3, low back pain projecting to distant territories (*e.g*. thigh, leg); 4, pure sciatica; 5, radiculopathy. P: Spearman R correlation coefficient. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Ultramicronized PEA is widely recognized to promote the resolution of neuroinflammation and exert neuroprotection. A substantial body of evidence indicates that neuroinflammation plays a prominent role in dopaminergic cell death; PEA proved to be an efficacious adjuvant therapy for Parkinson's disease, by slowing down disease progression and disability [21].

PEA is now considered to act *via* direct and indirect receptor pathways, redundantly involving both membrane-bound and nuclear receptors. Cannabinoid receptors type 1 and 2 (CB1 and CB2), cannabinoid-like G-coupled receptors GPR55 and GPR119, Transient Receptor Potential Vanilloid Receptor type 1 (TRPV1) channels and nuclear Peroxisome Proliferator Activated Receptor-alpha (PPAR-α) are the PEA molecular targets studied most [19]. Mast cells and microglia are among the most widely recognized cellular targets of PEA [22, 23]. These immune-inflammatory cells are primary interlocutors for pain neurons at both the peripheral and spinal/supraspinal levels [24]. Down-modulation of mast cells and microglia hyper-reactivity by PEA has been shown to relieve neuropathic pain in a number of experimental models [25, 26]. In a controlled study involving 42 patients with carpal tunnel syndrome, ultramicronized PEA (600 mg twice daily), administered both before and after surgery, reduced pain and improved sleep quality [27].

The present analysis yielded an NNT value of 1.7 for PEA 600 mg daily, which is, according to the main guidelines on neuropathic pain treatment, considerably better than that of first-line drugs [28, 29]. TCAs yielded a score of 3.5, SNRIs of 6.4, gabapentin of 7.2 and pregabalin of 7.7. As regards low back pain, in particular, duloxetine and some other antidepressants have been tried successfully [30]. However, when a recent meta-analysis compared duloxetine with other widely prescribed drugs, including NSAIDs and scheduled and non-scheduled opioids, as well as with other antidepressants, the estimated treatment difference yielded a negligible magnitude of effect for all the treatments (standardized mean difference <0.2) [29]. Indeed, the existing guidelines and meta-analyses for low back pain favor physical treatments, recommending the use of drugs only after their failure. The only classes of drugs that are mentioned are NSAIDs and opioids [31, 32], both of which are known to be associated with safety problems if used chronically. Although novel therapeutic strategies and new target receptors are currently being investigated, the evidence is still poor [33, 34].

By contrast, PEA has been shown to be totally safe and to have a non-significant (and indeed infinite) number needed to harm. This is in line with the toxicological profile of micronized PEA, whose LD50 is greater than 2000 mg/kg body weight for acute oral toxicity and NOEL (no treatment-related adverse effects) > 1000 mg/kg body weight for sub-chronic toxicity [35].

The remarkable NNT value of PEA, which is considerably better than that of first-line treatments, should be judged bearing in mind the possible sources of bias described in the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Table **2**) [36]. Last but not least, despite coming from a large cohort of patients from different sites, the results are all included in the same study.

Table 2. Bias examination.

Methodological Items	Guida *et al*., 2010
Random sequence generation	Low Risk
Allocation concealment	Uncertain Risk
Blinding of participants and personnel	Low Risk
Blinding of outcome assessment	Low Risk
Incomplete outcome data	Low Risk
Selective reporting	Uncertain Risk
Other bias	Low Risk

Finally, it should be kept in mind that the original study by Guida and colleagues [13] may be biased by the inclusion of patients suffering from either acute or chronic sciatica. Depending on the studies, complete recovery from acute sciatica varied greatly, ranging from four weeks to 12 months [37, 38].

Owing to the short duration of the original study [13] (three weeks), an unpredictable number of participants might have experienced spontaneous recovery. Although this holds true both for placebo and treated patients, it still might have impacted our NNT analysis.

4.1. Correlation between Efficacy and Probability of Neuropathic Pain

We found a significant correlation between the increasing probability of neuropathic pain and pain relief. This result confirms the efficacy of PEA on neuropathic pain, which has been demonstrated by several studies in both experimental models [39-41] and in humans [42-49, 27]. By contrast, we did not observe any such correlation between the probability of neuropathic pain and an improvement in function. This finding was not, however, unexpected. Functional impairment may, on the one hand, be affected by a number of clinical and psychological factors and depend on neuropathic pain, on nociceptive pain, on a combination of both or on the degree of the inflammatory response. On the other hand, PEA is known to underlie a wide range of biological functions [18]. We may thus conclude that although PEA treatment significantly improved the disability score in the study population, this happened regardless of the nature of pain.

One important limitation of the present analysis is that the five categories of increasing probability of neuropathic pain were decided "a posteriori", *i.e*. study patients were not originally categorized according to the likelihood of neuropathic pain. It must, however, be stressed that the patients were assigned to one of the five categories by two blinded clinicians on the basis of objective criteria.

CONCLUSION

In the present post hoc analysis, we reanalyzed the data from Guida *et al.*'s study [13] to assess the clinical importance of PEA treatment and understand whether PEA was similarly effective on both the nociceptive and neuropathic components of pain. The clinical relevance was confirmed by calculating the NNTs for pain and function. We assigned each patient to one of the five categories of increasing probability of neuropathic pain and assessed any correlation between the improvement in pain and function with these five classes. According to our reassessment, PEA appears to be an ideal candidate for the treatment of mixed pains, such as low back pain with sciatica. Although the NNT values may be dampened by the existence of sources of bias in the original study, PEA not only proved to be extremely effective on both pain and function but was also tolerated extremely well.

LIST OF ABBREVIATIONS

NNH = Number Needed to Harm

NNT = Number Needed to Treat

PEA = Palmitoylethanolamide

RMDQ = Rolan-Morris Disability Questionnaire

VAS = Visual Analog Scale

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

Giorgio Cruccu received a research grant, consulting fees and payments for lectures from Sigma-Tau of ALFASIGMA Group, and consulting fees from Angelini, Biogen, and Mundipharma. Giulia Di Stefano has no conflicts to declare. Paolo Marchettini has been acting as lecturer and advisor for Pfizer Italy S.p.A., FB HEALTH S.p.A, Chiesi Italia S.p.A. Andrea Truini received consulting fees or payment for lectures from Sigma Tau of ALFASIGMA Group, Angelini, Gruenenthal and Pfizer.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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