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Palmitoylethanolamide in the Treatment of Chronic Pain Caused by Different Etiopathogenesis

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Abstract

Objective. To assess the efficacy and safety of palmitoylethanolamide (PEA), an endogenous fatty acid amide belonging to the N-acylethanolamines family, in reducing pain severity in patients with pain associated to different pathological conditions.

Methods. This was an observational study conducted on 610 patients who were unable to effectively control chronic pain with standard therapies. PEA (600 mg) was administered twice daily for 3 weeks followed by single daily dosing for 4 weeks, in addition to standard analgesic therapies or as single therapy. The primary outcome measure was the mean score pain severity evaluated by the numeric rating scale. Safety was also evaluated.

Results. PEA treatment significantly decreased the mean score pain intensity evaluated in all patients who completed the study. The PEA effect was independent of the pain associated pathological condition. PEA-induced decrease of pain intensity was present also in patients without concomitant analgesic therapy. Importantly, PEA showed no adverse effects.

Conclusions. In this study, PEA was effective and safe in the management of chronic pain in different pathological conditions.

Key Words. Chronic Pain; Pain Management; Palmitoylethanolamide; Immune Cells

Introduction

Chronic pain is an expression of maladaptive alterations in the somatosensory system, which outlasts its biological usefulness and often can be considered a disease on its own right. Chronic and neuropathic pain can adversely affect a patient's overall health-related quality of life [1–4], including physical and emotional functioning, and is associated with substantial societal costs [5–7]. Chronic pain is challenging to manage, and many patients have pain that is refractory to existing treatments [6,8–10]. Numerous randomized clinical trials have shown that no more than half of patients experience clinically relevant pain relief, which is almost always partial but not complete. In addition, patients frequently experience burdensome adverse effects and, as a consequence, are often unable to tolerate the treatment [6,9,11,12]. Alternative, efficacious, and safe analgesic agents represent an important unmet medical need.

Current chronic pain management relies heavily on agents long known to have analgesic properties. More recently, other medicines have entered the scene, such as antidepressants and anticonvulsants, drugs that relieve pain mainly by acting on neurons. Further approaches to the treatment of chronic pain that focus on targeting the underlying mechanism(s) [12,13] may reveal novel modes of action for therapeutic development.

To better appreciate the molecular mechanisms of pain, one must recognize that chronic pain can originate from neuronal tissue damage or nervous system dysfunction. Although pain is processed in the nervous system, the immune system, such us mast cells and microglia, also contribute to chronic pain hypersensitivity [14]. Mast cells and other immune cells infiltrate damaged peripheral nerves. Immune activation and nociceptor sensitization after nerve injury initiates the release of mediators that activate Toll-like receptors on mast cells close to the nerve terminal. Vasodilators are also released, promoting adhesion and transmigration of immune cells including T cells, neutrophils and monocytes, and recruitment of macrophages. These cells, once activated, release a battery of inflammatory mediators that act on receptors expressed on adjacent nociceptor nerve terminals, leading to peripheral nociceptor sensitization and enhanced responsiveness of central nervous system (CNS) neurons. Thus, resident mast cells sensitize peripheral receptors.

Pain can thus occur spontaneously, be evoked by stimuli that are normally not painful, and be enhanced by normally noxious stimuli [15]. The persistent and aberrant excitability of primary sensory ganglia might also activate spinal microglia, the resident macrophages of the CNS [16]. Following peripheral nociceptive activation via nerve injury, microglia become activated and release pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, thereby initiating the pain process. Microglia propagate neuroinflammation by recruiting other microglia and eventually activating nearby astrocytes, thereby prolonging the inflammatory state and leading to a chronic pain condition. The contribution of mast cells and microglia in the development and progression of chronic pain proposes that these cells represent new and innovative targets for chronic pain control [17–19].

Peripheral and/or central immune cell participation is a key element of the molecular processes associated with chronic pain [20,21], raising the possibility that modulation of these cells' activation might be efficacious in chronic pain independent of etiopathogenesis. Yet, in spite of mounting evidence, pharmacological approaches continue to target almost exclusively the glial cell element underlying enhanced hypersensitivity in chronic pain while ignoring the contribution of mast cells.

Palmitoylethanolamide (PEA), an endogenous fatty acid amide, is a congener of the endocannabinoid anandamide (AEA) that belongs to a class of lipid mediators, the superfamily of N-acylethanolamines [22]. PEA reportedly inhibits the release of pro-inflammatory mediators from activated mast cells [23,24] and reduces the recruitment and activation of mast cells at sites of nerve injury, events associated with anti-allodynic and anti-hyperalgesic effects in a model of neuropathic pain [25]. Moreover, after peripheral nerve injury as well as following spinal neuroinflammation or spinal cord injury, PEA treatment inhibited microglia activation [26–28] and the recruitment of mast cells into spinal cord [29]. PEA effects on chronic and neuropathic pain symptoms have been confirmed in numerous clinical conditions [30–36].

These observations prompted us to evaluate PEA effect on chronic pain associated with *different pathological conditions* in patients who were *undergoing standard therapies* with unsatisfactory results *or in those patients who discontinued standard therapy* because of important side effects. In addition, a positive outcome would support the concept of a common underlying inflammatory/algesic mechanism in the diverse pathological conditions studied, and which is amenable to PEA treatment—unlike currently used analgesics whose mode of action controls only singular components of systemic pain.

Methods

Study Participants

Our study spanned the period from January 2009 to January 2011, and involved a total of 610 outpatients (178 males and 432 females) affected by chronic pain due to different pathological conditions (Table 1). Patients were referred to the Pain Clinic of the Policlinico Tor Vergata in Rome to receive an adequate treatment. All 610 patients had been suffering for more than 6 months (with the exception of some patients affected by acute herpes zoster [HZ] infection) and were previously treated with conventional analgesic therapies: antidepressants, anticonvulsants, opioids, and non-steroidal anti-inflammatory drugs.

Table 1 Patient characteristics

Number of patients	610	
Male	178	
Female	432	
Age (years) mean ± standard deviation (SD)	65.6 ± 13.3 (minimum 19, maximum 90)	
Pain associated to:	Number of patients (%)	Age (years) mean ± SD
Radiculopathy	331 (54.3)	65.4 ± 13.9
Osteoarthrosis	54 (8.9)	69.1 ± 10.95
Herpes zoster infection (*acute*, *persistent phase*, and *post-herpetic neuralgia*)	44 (7.2)	72.6 ± 9.60*
Diabetic neuropathy	32 (5.4)	71.8 ± 9.58
Failed back surgery syndrome	76 (12.4)	62.9 ± 13.54
Oncologic diseases	22 (3.6)	65.0 ± 11.28
Other diseases	51 (8.3)	56.2 ± 15.80
Number of patients who completed the study	564 (92.5%)	
Number of dropouts†	46 (7.5%)	

* Age range of patients suffering from herpes zoster: 51–60 years (n = 6); 61–70 years (n = 10); 71–80 years (n = 20); 81–90 years (n = 8).

† Dropouts due to 1) good/satisfactory pain control (n = 16), 2) personal unspecified reasons (n = 20), 3) poor adhesion to therapy (n = 10).

The greater part of the patients (515), even if still under treatment, complained of poor pain control, while others (95) suspended therapy due to relevant side effects.

Patients having a pain score of ≥4, as evaluated by the numeric rating scale (NRS) and suffering from more than 6 months, were eligible for the study if they were ≥18 years old and able to comprehend subjective pain scales. Excluded from the study were patients aged <18 years, those having a pain intensity score <4 on NRS, pregnant females, patients with diseases attributable to psychiatric disorders and patients undergoing, or scheduled to undergo, physiotherapy, radiotherapy, or chemotherapeutic treatment.

The study was approved by the Independent Ethics Committee of Fondazione Policlinico Tor Vergata (Rome). All patients received a description of the study, prior to their giving written informed consent in accordance with the Declaration of Helsinki.

Study Design

An observational study was carried out according to standard accepted procedures in clinical practice. Eligible patients received PEA, a dietary food for special medical purposes (Normast® 600 mg, Epitech Group, Saccolongo, Padua, Italy) twice daily for 3 weeks followed by single daily dosing for 4 weeks. PEA was added to conventional analgesic therapies established at the baseline visit for each patient, administered as fixed doses throughout the entire observational period, or as single treatment if the patient had discontinued standard therapy because of noteworthy side effects and refused to continue treatment. PEA dosage was in the range of that used from previous experience; treatment period was extended because of pain severity and patient resistance to the standard treatments [30–32,34–36].

Outcome Measures

Before starting PEA treatment (baseline), the patients were instructed on how to use the NRS to rate level of pain (0–10: from no pain to worst imaginable pain). The NRS, a rating scale usually adopted in our clinical practice, is easy to administer and easily accepted by the patient. NRS assessment was performed at baseline and at the end of PEA treatment. In post-herpetic neuralgia (PHN) [37] patients only, the NRS was also measured after about 6 months from discontinuation of PEA treatment. In addition, 3 weeks after starting treatment (i.e., at the end of two tablets/day PEA), an informal telephone interview was carried out with all patients, to assess their adhesion to the therapy and their subjective clinical impression. Only in patients with HZ infection, the NRS was measured also after approximately 6 months from discontinuation of PEA treatment. This was done because of the severity of disease affecting these patients and their age bracket (Table 1)—both of which are responsible for chronic pain [38–40].

Safety Assessments

Safety was evaluated by measuring discontinuation rates, treatment-emergent adverse events, and serious adverse events.

Statistical Analysis

Data were expressed as the mean ± standard deviation and percentage, unless otherwise specified. Data were analyzed by means of mixed model repeated measures (MMRM) without the assumption of variances. Student's *t*-test was used to compare pain intensity between groups. A P value of <0.05 was considered statistically significant.

Results

All patients enrolled in this study were Caucasian with a mean age of 65.6 ± 13.3 (432 females and 178 males). Of the 610 patients enrolled, 564 completed the study while 46 (7.5%) patients withdrew for reasons unrelated to the treatments (Table 1). The percentage of patients dropping out was similar between those receiving PEA plus anticonvulsant and opioid or anticonvulsant and rescue drugs or PEA alone (Table 2). Patients who completed the study did not report any treatment-related adverse events or serious adverse events.

Baseline Clinical Characteristics

At the start of the study (baseline), most of the enrolled patients (476) were undergoing standard therapies for chronic pain (opioids, antidepressants, anticonvulsants, alone or in combination, and nonsteroidal anti-inflammatory drugs) with unsatisfactory results. These conventional therapies were adjusted according to dose, optimized and administered to each patient at a fixed dose throughout the entire observational period. In determining the appropriate dose, we considered the following factors: 1) the use of a low dose to manage side effects; and 2) the use of transdermal therapy (fentanyl and buprenorphine at the appropriate dose after titration) for those patients (mainly oncologic) whose general condition did not allow for oral therapy. The drugs utilized and their respective mean doses are reported in Table 3.

A group of patients (95) had previously discontinued standard therapy because of marked side effects. In this

Table 2 Dropout patients

Therapy	N	Dropout	%
PEA + anticonvulsant + opioid	430	32	7.44
PEA + anticonvulsant + rescue drugs	85	7	8.24
PEA	95	7	7.37
Total	610	46	7.54

Table 3 Mean dosage of opioids; anticonvulsants and rescue drugs used during the study period

—	Mean Dose
Anticonvulsant	
Gabapentin	1,832.43 mg/day
Pregabalin	222.89 mg/day
Opioid	
Oxycodone	16.74 mg/day
Hydromorphone	6.4 mg/day
Fentanyl TTS	21.42 μg/h
Buprenorphine TTS	24.5 μg/h
Rescue drug	
Paracetamol + Tramadol	1,000 mg + 59.03 mg/day

TTS = transdermal therapeutic system.

group, PEA was the only treatment for chronic pain. Chronic pain was associated to radiculopathy (R) caused by compression or lesion of a dorsal root or its ganglion, osteoarthrosis (OA), HZ infection as acute, persistent pain and PHN [37], diabetic neuropathy (DN), chronic back pain in patients who experienced a failed back surgery (FBSS) [41], oncologic diseases and other diseases (i.e., post-traumatic neuropathy, trigeminal neuralgia, algodystrophy, neuropathic pain associated to multiple sclerosis, brachial plexus injury, post-ictus conditions, polyneuropathy, syringomelia, Arnold syndrome, post-polio syndrome, Charlin syndrome, amyloidosis, back hemangioma, autoimmune myelitis, and neuropathic pain to the upper limb). Because only a few patients were affected by each of the above diseases, we have grouped them together (Table 1).

If considering patients in relation to concomitant therapies (Cth), the two groups, independent of their receiving or not standard therapy (PEA+Cth and PEA groups), displayed similar characteristics both in the distribution of different conditions where pain was associated and in relation to the range of NRS (Table 4). The most frequent pain intensity score ranged from 6 to 7, a value observed in 51% of all cases. The NRS mean value of all patients at baseline was 6.4 ± 1.4 (Table 5). A NRS mean value of >6 was observed in all the different pathological conditions. The NRS baseline mean values in the PEA+Cth and PEA groups were 6.4 ± 1.4 and 6.5 ± 1.2, respectively (Table 5).

Analysis of PEA Effect in All Patients

PEA treatment markedly decreased the mean score pain intensity evaluated in all patients who completed the study. In fact, NRS mean value decreased from a baseline of 6.4 ± 1.4 to 2.5 ± 1.3 at treatment end. The MMRM analysis, which takes into account variables such as age, gender, and type of pathological condition, showed that PEA treatment was the only variable to significantly account for the differences between the means obtained at treatment end vs baseline ($P = 0.0001$). In addition, none of the other considered variables interfered with the PEA effect, including concomitant therapies. These results were confirmed by analyzing the PEA effect in relation to the different pathological conditions where pain was associated: the reduction of pain intensity was highly and equally significant in all patient groups (Figure 1).

Patients with pain due to HZ infection (Table 1) were subdivided into three groups, depending on the start of the

Table 4 Distribution of patients in relation to pain etiology and range of NRS

Patients	Total N (%)	PEA+Cth N (%)	PEA N (%)
Total	610 (100)	476 (100)	95 (100)
Pain etiology			
Radiculopathy	331 (54.3)	285 (55.3)	46 (48.4)
Osteoarthrosis	54 (8.9)	43 (8.3)	11 (11.6)
HZ	44 (7.2)	38 (7.4)	6 (6.3)
DN	32 (5.3)	23 (4.5)	9 (9.5)
FBSS	76 (12.4)	62 (12.0)	14 (14.7)
Oncologic diseases	22 (3.6)	21 (4.1)	1 (1.0)
Other diseases	51 (8.3)	43 (8.4)	8 (8.4)
Range NRS			
4–5	172 (28)	146 (28)	26 (27)
6–7	310 (51)	261 (51)	49 (52)
8–10	128 (21)	108 (21)	20 (21)

HZ = herpes zoster infection; DN = diabetic neuropathy; FBSS = failure back surgery syndrome; NRS = numeric rating scale; PEA = palmitoylethanolamide; Cth = concomitant therapies.

Table 5 NRS baseline values in all patients and in patients grouped for pathological conditions where pain was associated and for the type of treatment administered

NRS	Mean ± Standard Deviation
Total	6.4 ± 1.4
Radiculopathy	6.4 ± 1.4
Osteoarthrosis	6.0 ± 1.3
HZ	6.2 ± 1.5
DN	6.6 ± 1.3
FBSS	6.5 ± 1.5
Oncologic diseases	6.4 ± 1.4
Other diseases	6.7 ± 1.1
PEA+Cth	6.4 ± 1.4
PEA	6.5 ± 1.3

HZ = herpes zoster infection; DN = diabetic neuropathy; FBSS = failed back surgery syndrome NRS = numeric rating scale; PEA = palmitoylethanolamide; Cth = concomitant therapy.

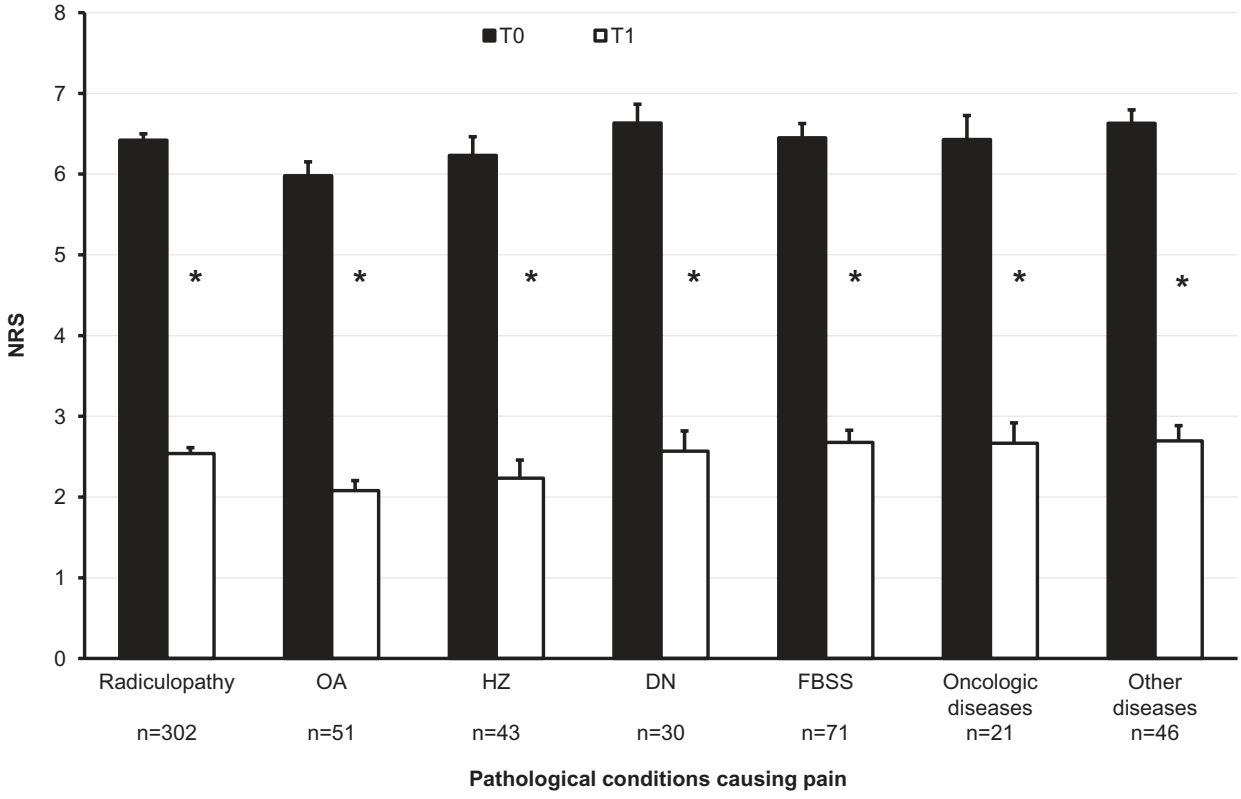

Figure 1 Reduction of pain intensity following palmitoylethanolamide (PEA) treatment in patients with chronic pain associated to different pathological conditions. T0 = Baseline (start of PEA treatment); T1 = end of PEA treatment. Numerical rating scale (NRS) values are expressed as mean ± standard error. * $P < 0.0001$ vs baseline. OA = osteoarthrosis; HZ = herpes zoster infection; DN = diabetic neuropathy; FBSS = failed back surgery syndrome.

treatment in relation to infection onset. The efficacy of PEA was seen to depend on the disease phase. In fact, when MMRM analysis was performed, treating as variable the disease phase, patients who started PEA treatment in the acute phase (within the first 3 months of viral infection) had a more marked and statistically significant ($P = 0.0183$) decrease of pain intensity as compared with those who started PEA treatment in the persistent phase (within the 3rd to 6th month from onset), and after the 6th month (PHN) (Figure 2). In addition, in these patients, the reduction of pain was maintained also 6 months after discontinuation of PEA treatment (Figure 2).

Effect of PEA in Patients Without Standard Therapy for Chronic Pain

The MMRM analysis of all patients receiving PEA treatment revealed the absence of interference of concomitant analgesic therapies in the PEA-induced reduction of chronic pain. However, the availability of a group of patients without concomitant therapy also allowed an analysis of PEA effects separately. In patients without concomitant analgesics, PEA was equally efficacious in reducing chronic pain. The degree of such a reduction was similar to that observed in patients who had concomitant analgesic therapies (Figure 3). Comparing baseline mean pain score value with that obtained at treatment end, a highly significant difference ($P < 0.0001$) was seen in both the PEA+Cth and the PEA groups. This observation was confirmed by evaluating the difference between the effects observed in two groups ($P < 0.6245$ unequal variance *t*-test).

Discussion

Our results demonstrate that significantly reduced pain intensity could be achieved by: PEA addition to ongoing standard therapies for chronic pain in patients with unsatisfactory management of pain relief or PEA treatment in patients who had discontinued standard therapy because of side effects. Moreover, PEA treatment was efficacious in patients with chronic pain associated to a variety of pathological conditions and undergoing standard analgesic therapy targeting mainly neurons.

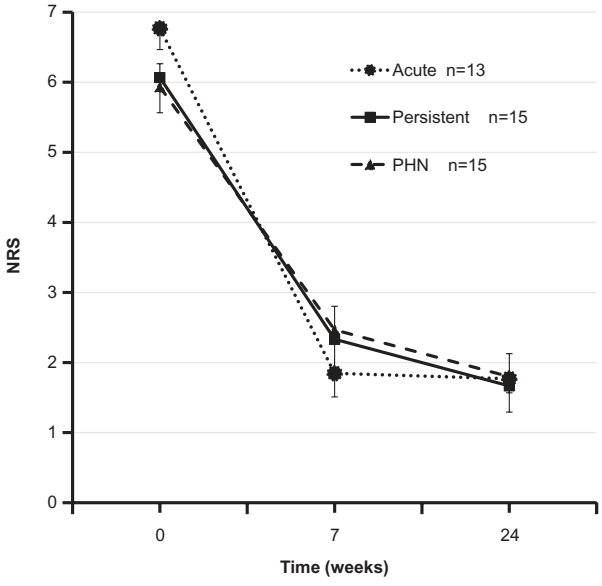

Figure 2 Reduction of pain intensity in patients with HZ, acute, persistent phase and PHN. Numerical rating scale (NRS) values are mean ± standard error. $P = 0.0183$ for acute phase when mixed model repeated measures (MMRM) analysis was performed considering as variable the phases of disease. All patients, with the exception of 10 belonging to the PHN group, were also evaluated 24 weeks after treatment discontinuation.

Pharmacotherapy for chronic pain should ideally be based on the mechanisms underlying clinical pain presentations. Developing therapies which control mechanisms that are common to different conditions associated with chronic pain is certainly not a mutually exclusive proposition. Current strategies comprise, for example, glial inhibitors with anti-inflammatory properties, or apparent selectivity in inhibiting glial metabolism; agents targeting mast cell activation [17]. Both limited in scope and may carry issues of toxicity/tolerability. While a basic characteristic of chronic pain is a lesion or dysfunction of somatosensory neurons [42], nerve injury often leads also to inflammatory reactions that mobilize the immune system. In particular, mast cells orchestrate inflammatory responses in peripheral nervous tissues, with microglia doing the same in spinal cord [15,43]. Thus, a drug therapy that targets complementary pathways or mechanisms might result in more efficacious pain relief, especially in those cases that are refractory to standard therapy which acts only on neurons.

Our results confirm and extend previous findings in which patients with chronic pain due to DN or PHN, treated with PEA and pregabalin (dose escalation from inactive to therapeutic), brought about pain relief, an effect paralleled by a reduction of functional disability, already evident with a subthreshold dosage of pregabalin [32]. Moreover, PEA-induced pain relief was independent of the condition where pain was associated. It is believed that PEA elicits its anti-inflammatory and analgesic activities mainly by modulating mast cell [25] and microglia activation [27,29]. This PEA effect reinforces the important role for mast cell and microglia activation in these conditions. The infiltration of inflammatory cells observed in human sensory ganglia following natural varicella-zoster virus reactivation supports this view (HZ) [44]. Although mast cells were not among the inflammatory cells infiltrating ganglia of PHN patients, they are normally located around spinal ganglia [45] and within the nerve [46]. Following nerve injury, mast cell numbers increase, and their phenotype changes from quiescent with compacted granules to degranulated [25,47,48]. An increase in mast cells was reported in nerve roots showing Wallerian degeneration following experimental lumbar nerve root compression [49]. Mast cells are also numerous in the granulation tissue zones of painful discs as compared with non-granulation tissue zones or aging discs and normal control discs [50].

The involvement of mast cells in the development of DN has been long known, with their proliferation being reported in peripheral nerves of streptozotocin diabetic rats [51]. Alterations partly attributable to abnormal mast cell activation, such as ultrastructural abnormalities in Schwann cells encompassing the full range of reactive, degenerative and proliferative changes as described in galactose-fed rats were reported in sural nerve biopsy

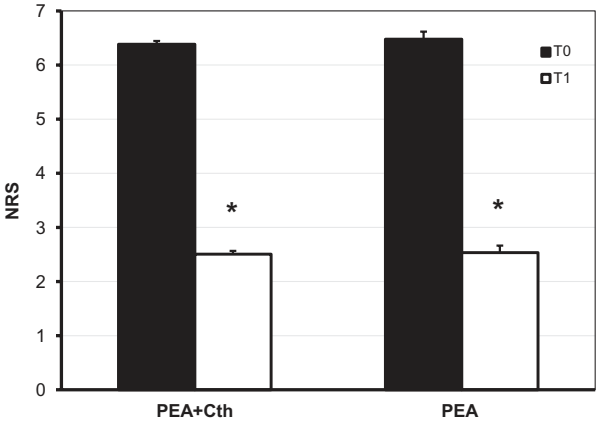

Figure 3 Reduction of pain intensity following palmitoylethanolamide (PEA) treatment in patients with (PEA+Cth) and without (PEA) concomitant therapy. T0 = Baseline (start of PEA treatment); T1 = end of PEA treatment. Numerical rating scale (NRS) values are mean ± standard error. *$P < 0.0001$ vs baseline *t*-test. Four hundred seventy-six patients were treated with PEA+Cth, and 88 patients received PEA only.

samples from patients with diabetes and progressive worsening of neuropathy [46,52]. An abnormal activation of mast cells is frequent in cancer patients; mast cells typically accumulate at the periphery of tumors, and a large body of evidence supports a negative role for mast cells in tumorigenesis [53]. Mast cells activated by nerve injury may contribute to chemotherapy-induced peripheral neuropathy and chronic pain [54]. Peripheral activation of mast cells and other immune cells associated with sensitization of peripheral nociceptors may trigger spinal microglia activation [18]. For example, microglia activation in the spinal cord has been reported in models of lumbar radiculopathy [55] and in painful disc herniation [56,57], as well as in the spinal cord of streptozotocin diabetic rats [58]. There is little direct evidence of glia activation in human conditions associated with chronic or neuropathic pain; however, glia are hypothesized to be least partially responsible for inducing pain spikes by attempting to reactivate unresponsive neurons [59].

Activation of mast cells and the systemic release of histamine as well as glial activation are common side effects of opiates such as codeine and morphine. The activation of these immune cells may either compromise the efficacy of opioids or contribute to their side effects [60–62].

A key point emerging from the present study is the ability of PEA to reduce pain intensity also in patients without concomitant therapies. This group consisted of patients who failed to respond or who were unable to tolerate standard therapies. The efficacy of PEA in this group confirms that its actions are independent from those of other therapies and suggests that the concomitant control of mast cell activity in the periphery and microglia activation in the CNS may significantly reduce the intensity of chronic and/or neuropathic pain.

There is an emerging realization that glia, and microglia in particular, constitute an important source of inflammatory mediators and may have a fundamental role in neuropathic pain. Microglia respond also to pro-inflammatory signals released from other non-neuronal cells, principally those of immune origin. Mast cells are of particular relevance in this context. Because patients suffering from chronic pain are often unresponsive to therapies which hit neurons, the glia–mast cell axis presents a highly attractive target for intervention.

Moreover, our results raise the possibility that PEA by itself might be efficaciously in chronic or neuropathic pain. The ability of PEA to reduce chronic pain has been demonstrated in patients affected by lumbosciatica [34,63] and in patients with chronic pelvic pain associated to endometriosis [33,35]. Moreover, in patients affected by carpal tunnel syndrome and those with peripheral neuropathy, PEA-induced reduction of pain was associated with an improvement of neuronal functional parameters such as motor distal latency and action potential amplitudes measured by laser-evoked potentials, thus suggesting that PEA effects are not exclusively symptomatic [36,64]. Given the observational nature of the present study, it will be important to determine in the future a role, if any, for a placebo effect as well as the possibility that simply participating in the study may have had some beneficial effect by providing patients with chronic pain additional support. However, the numerous positive reports of PEA-induced pain reduction [65] would seem to argue against this.

The present findings merit particular interest in view of the complete absence of side effects ascribed to PEA, as confirmed in numerous clinical studies that evaluated PEA as a prophylactic for respiratory diseases both in children and in adults. In these studies, children had no adverse effects, and all biochemical and hematochemical parameters in adults were unaffected by PEA treatment [66–69]. Guida et al. [34] confirmed the good tolerability of PEA in a study assessing PEA in patients with chronic pain due to lumbosciatica.

In summary, we have confirmed the efficacy of PEA to reduce chronic pain and extend this observation to different pain-associated pathological conditions. PEA was efficacious not only in patients challenged to effectively control chronic pain with concomitant standard but also in patients without standard therapy.

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