New Targets in Pain, Non-Neuronal Cells, and the Role of Palmitoylethanolamide

Jan M. Keppel Hesselink*

Department of Pharmacology and Toxicology, University of Witten/Herdecke, Germany

Abstract: Persistent pain in neuropathic conditions is often quite refractory to conventional analgesic therapy, with most patients obtaining, at best, only partial relief of symptoms. The tendency still exists to treat these complex pains with one or a combination of two analgesics at the most. Given the complex nature of the underlying pathogenesis, this approach more often than not fails to produce a meaningful improvement. New targets are therefore badly needed. In this regard non-neuronal cells – glia and mast cells in particular - are emerging as new targets for the treatment of neuropathic pain. An extensive preclinical database exists showing that the naturally occurring fatty acid amide palmitoylethanolamide is endowed with anti-inflammatory activity, and clinical trials assessing the efficacy and safety of palmitoylethanolamide in neuropathic pain have been successful in generating proof-of-concept for treatment in man. Here I will review salient preclinical and clinical evidence supporting non-neuronal cells as viable targets in the treatment of neuropathic pain. This will be followed by a discussion of recent proof-of-concept clinical trials demonstrating the efficacy and safety of palmitoylethanolamide in the treatment of various neuropathic pain states.

Keywords: New targets, pain, non-neuronal cells, palmitoylethanolamide.

EMERGENCE OF A MULTI-MODEL THERAPY FOR PAIN

The pharmacotherapy of pain is evolving from a step-by-step approach to a multimodal therapy which, I believe, is destined to become the hallmark in how we treat neuropathic pain in the future. However, the literature at present provides little guidance on a suitable treatment regimen to follow. Current focus remains on the modulation of functions of the nervous system itself, especially ion channels, without taking other players into consideration - glia, mast cells, and other immune-competent cells. This is unfortunate, as the major players in the pathogenesis of chronic neuropathic pain most probably are these non-neuronal cells. [1-6]

Generally, there is a hierarchy of treatments for neuropathic pain physicians will mostly follow, starting often with monotherapy and increasing to maximal tolerated dose. When high-dose monotherapy proves insufficient or intolerable side effects prevent optimal pain control, combinations of various pharmacologic compounds follow next. The latter may comprise combining serotonin-noradrenaline uptake inhibitors, tricyclic antidepressants, anticonvulsants, opioids, natural and synthetic derivatives from Cannabis, endocannabinoids and topical analgesics. [7-10]

Most clinical studies have been conducted in painful polyneuropathy associated with diabetes, followed by postherpetic neuralgia. Studies in other types of neuropathic pain, such as pain in chronic idiopathic axonal polyneuropa thy, chemotherapy-induced pain and central neuropathic pain as in stroke and multiple sclerosis (MS) are rare; even more rare are studies in spinal pain syndromes.

THE STATIC NATURE OF ANALGESIC THERAPEUTIC EFFICACY

Although our understanding of neuropathic pain-generating mechanisms has advanced considerably since 2000, there has not been a corresponding improvement in treatment efficacy. Opiates and drugs such as amitriptyline remain unsurpassed as therapeutics.

Finnerup *et al*., [11] evaluated the 69 randomized controlled trials published in the past 5 years and compared these to the 105 trials published in the preceding 39 years. Their conclusion was intriguing: no real improvement in the treatment of neuropathic pain has been achieved, and recent clinical trials of older analgesics seem even to show an increase in numbers needed to treat (NNT)[1].

These authors further analyzed all completed clinical trials to date, to identify negative trials and publication bias. In addition to the published trials, their database presented one trial examining gabapentin 3600 mg, which relieved painful polyneuropathy with an NNT of 7.0 (4.3–20), as well as four positive and three negative trials with pregabalin, revealing a combined NNT of 9.5 (6.8–16.0). The observations imply that the figures most often quoted on NNT's of analgesics are *flawed;* these analgesics might be even less efficacious than previously thought. This fact, together with

*Address correspondence to this author at the Institute for Neuropathic Pain, Bosch en Duin, the Netherlands; Tel: 0031-6-51700527;
E-mails: jan@neuropathie.nu; info@ores.nl

[1] The NNT is the average number of patients who need to be treated to prevent one additional bad outcome (i.e. the number of patients that need to be treated for one to benefit compared with a control in a clinical trial).

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the relative high numbers needed to harm[2] makes one working in this field quite humble [12].

It is clear, especially for scientists working in the field of drug targeting, that most, if not nearly all of the current analgesics have one thing in common: targets are most often ion channels or surface receptors of neurons. [13-15] In this regard, non-neuronal cells and nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) have emerged as important targets in a variety of pain states. [4, 5, 16-18] In this short review we will address some aspects in this emerging field related to non-neuronal targets in chronic and neuropathic pain.

NON-NEURONAL CELLS AS NEW TARGETS FOR NEUROPATHIC PAIN

Today, there is good evidence that the major players in the pathogenesis of chronic neuropathic pain most probably are non-neuronal cells. [1-6] Mast cells, for example, have been the recognized to play a causative role in the development of hyperalgesia following nerve injury, [19] and their pathogenic involvement has also been demonstrated in chronic low back pain, [20] visceral or pelvic pain, [21-25] and migraine. [26-28]. Moreover, mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. [29] Together with glia, and especially microglia that are known to functionally interact with mast cells, [30] these immune cell types are now considered to be key to the phenomena of central and peripheral sensitization. [1-6].

Garrison *et al*., [31] were the first to demonstrate that after a unilateral ligation of nervous ischiadicus, unilaterally spinal glia became activated, swollen and a new phenotype of activated glia induced. This observation was soon followed by comparable findings in a variety of other studies. [32,33] Peripheral nerve injuries induce a low-grade inflammation in the dorsal horns of spinal cord and along the pain pathways to the thalamus and further to the parietal cortex, [34] due to the activation of Schwann cells, glial cells (especially microglia), and the production of cytokines and other inflammatory mediators within the PNS and CNS. [35-38] Such neuroinflammatory activity leads to the consolidation of the winding up phenomena, the central and peripheral sensitization. [39] Schwann cells, glia, microglia and astrocytes therefore play a central role in the pathogenesis of neuropathic and chronic pain. Gliopathic pain or asteropathic pain might even become new synonyms for neuropathic pain. There are data to support chronic pain syndromes such as rheumatoid arthritis and fibromyalgia as also linked to glia cell activation. [40-43]

Interestingly, also breakthrough pain (i.e., the transient exacerbation of pain experienced by a patient with relatively stable and controlled baseline pain) has been hypothesized to be due, at least in part, to glia hyper-reactivity. [44]

In a recent hallmark paper by Ohara *et al*., [45] the term 'gliopathic pain' indeed was coined. Glia, astrocytes and other immunocompetent cells directly influence neurotransmission between two neurons, and the recently introduced terminology 'pentapartite synapse' indicates the profound influence of these non-neuronal cells on neurotransmission. [46, 47] Glia-modulating drugs will therefore become a new class of analgesics, enhancing our pharmacotherapeutic armamentarium. [3,44, 48, 49] The first prototype is already available for human use. It is the endogenous fatty acid amide palmitoylethanolamide (PEA), and in more than 20 clinical trials the efficacy and safety of this compound have been documented and will be discussed later in this article. Thus, proof-of-principle (POP) for non-neuronal cells as targets in neuropathic pain has been established. Because many of these clinical studies have been published in Italian or Spanish journals, and the English speaking community might have missed this important new chapter in the treatment of chronic pain, we now focus on the endogenous non-neuronal cell modulator PEA.

PEA - AN ENDOGENOUS ANALGESIC AND MODULATOR OF GLIA AND MAST CELLS

PEA is a naturally occurring fatty acid amide belonging to the class of endocannabinoids which include, among others anandamide, oleoylethanolamide, stearoylethanolamide and lauroylethanolamide.

Amide lipids like PEA are widely distributed in nature, in a variety of plant, invertebrate, and mammalian tissues. [50, 51]

PEA is available in some European countries (Italy, Spain, the Netherlands, and since 2011 also in Germany) for the treatment of chronic pain and chronic inflammation, as a diet food for medical purposes (Normast ^{TM}). [52]

PEA first attracted attention in 1957, with its isolation from soybeans, peanuts, and egg yolk and identification of anti-inflammatory activity [53]. PEA is produced on demand and accumulates locally during several inflammatory and painful disorders, e.g. intestinal inflammation, [54] chronic migraine, [55] neuropathic pain, [56, 57] cerebral ischemia [58] and MS. [59] Increase in PEA local levels is unquestionably considered to play protective and pro-homeostatic roles. [60] PEA exerts anti-inflammatory and anti-hyperalgesic effects in various animal models of inflammation and pain [60, 61] and it has been suggested to function as an endogenous regulator of nociception. [62]

Since the first paper on PEA was indexed in Pumed in 1968 [63] nearly 300 entries have appeared, under the keyword 'palmitoylethanolamide'. In the 1990s the relationship between anandamide and PEA was first described, with growing insight into the function of the endocannabinoids such as oleamide, 2-lineoylglycerol, 2-palmitoylglycerol, and investigation into their capacity to modulate pain sensitivity and inflammation. [64] In the course of these studies it emerged that PEA could alleviate, in a dose-dependent manner, pain behaviors elicited in mouse pain models and down-regulate mast cell hyperactivity. [65, 66]

Mast cells are immunocompetent cells often found in proximity to sensory nerve endings. Their degranulation (i.e. the release of dozens of bioactive mediators stored in intracellular granules) can enhance the nociceptive signal, which is why peripheral mast cells are considered to be pro-inflammatory and pro-nociceptive. [67] For example, mast cells synthesize, store and release nerve growth factor, [68]

[2] The number needed to harm (NNH) is similar to NNT and indicates how many patients need to be exposed to a risk factor to cause harm in one patient who would not otherwise have been harmed. The lower the NNH, the worse the risk factor.

which itself produces inflammation and sensitization of the peripheral terminals of sensory neurons. [69] Mast cells are found also in the spinal dura, the thalamus and the dura mater. [67, 70] Conceivably, PEA may represent a new therapeutic approach for migraine, as meningeal nociceptors can be activated locally through a neuroimmune interaction with resident mast cells populating the dura mater. [27] Human mast cells release a vast array of mediators, which may well account for the mast cell's broad involvement in physiological and pathophysiological functions and diseases. Mast cell modulation by PEA might thus be relevant for disorders such as bladder pain, pelvic, pain, sciatic pain, headache, postsurgical pain, prostate pain and male infertility, chronic regional pain syndrome (CRPS), burning mouth syndrome, and mast cell activation syndrome, among others. [25, 29, 71-80]

Indeed, there are numerous examples of PEA down-modulation of mast cells *in vitro* and *in vivo*, resulting in decreased release of various bioactive mediators (i.e., histamine, tumor necrosis factor-alpha, prostaglandins, nerve growth factor, serotonin). [81-84] This, in turn, produced clinical effects such as pain relief and better motor function after spinal cord injury. [66, 84-87]

Furthermore, PEA protects microglial cells from excitotoxicity, [88] Microglia possess the machinery to synthesize and hydrolyze PEA. [89] PEA is able to control the microglial behaviour [58, 90] and revert microglial hyperactivation in the spinal cord during experimental neuropathic pain, suggesting targeted glial effects of PEA in the CNS of chronic pain-affected subjects. [91]

MAIN TARGET OF PEA: PPAR-α

PEA mechanism(s) of action is still a matter of debate, although it seems that the antinociceptive effect is mediated by multiple mechanisms (i.e., multimodal mechanism of action). [60] Membrane receptors (i.e., cannabinoid receptors), [81] nuclear receptors (i.e. PPAR), [92, 93] neurosteroid synthesis, [94] mast cell down-modulation [82, 86, 87] and control of microglial activation [91] are all purported mechanisms of action of PEA. These may coexist, depending upon the physiological and pathophysiological circumstances. [95]

A separate effect, the so called entourage-effect, has been used to explain PEA biological activities. [96, 97] Although PEA affinity for cannabinoid CB1 and CB2 receptors is very low, [98] its antinocicepive effects are prevented by the cannabinoid receptor antagonists. [65, 99] Thus when referring to PEA, it is now preferable to use the term "cannabimimetic compound" or "indirect endocannabinoid" [100].

Although PEA has affinity for other PPAR isoforms, G-coupled receptors, novel cannabinoid receptors, and receptors GPR55 and GPR119 with an unknown function, [92, 101-103] PPAR-α may be the main biological target of PEA.

PEA up-regulates PPAR-α in a model of spinal cord injury. [87] In this injury model, PPAR-α is down-regulated, resulting in activation of inflammatory cascades leading to tissue destruction. PPAR-α activation by PEA inhibits these detrimental cascades. Delta9-tetrahydrocannabinol also exerts neuroprotective properties, most probably via a PPAR-α mechanism of action. [104] PEA up-regulation of PPAR-α results in decreased output of inflammatory mediators like tumor necrosis factor-α and interleukins, thus supporting PEA's role as a modulator of inflammation and pain. [87] Activation of PPAR-α is neuroprotective and, more generally cytoprotective in a number of animal models. [104-106] PEA also reduces neurological deficits in a spinal trauma model, via reduction of mast cell infiltration and activation. [87]

The concept of lipid N-acylethanolamines such as PEA acting in an autocoid manner to control mast cell activation was first proposed by the Nobel laureate Rita Levi-Montalcini in 1993, [107] using the acronym ALIA (Autacoid Local Injury Antagonism). [81,107] Under this nomenclature lipid amides like PEA are classified as ALIAmides, beingautocoids (regulating molecules) locally produced and acting locally. In this sense prostaglandins are also classified as autocoids. In the case of ALIAmide, these autocoids are synthesized in response to injury or inflammation, to counteract such pathology. The period 1993-2011 has seen numerous publications dealing with the modulatory effects of PEA on mast cells. [81-87,108,109]

PEA affinity for PPAR-α, coupled with the widespread presence of this receptor in CNS microglia and astrocytes (which play a key role in the winding up phenomena, based on peripheral and central sensitization [110]) provides a strong underlying rationale for PEA application in the treatment of neuropathic pain. [111-114] Further, PEA performed better in the so-called mice forced swimming test compared to the anti-depressant fluoxetine. [115] PEA anti-inflammatory action counteracted reactive astrogliosis induced by beta-amyloid peptide in a rodent model relevant for neurodegeneration, most probably via PPAR-α. [116] In models of stroke, MS and other CNS trauma settings, PEA displayed neuroprotective properties. [59, 87, 112, 113] At the clinical level, in Italy for example, neurologists have used this preclinical evidence as the impetus to treat patients suffering from a variety of disorders, from MS to neuropathic pain. [18, 61, 62, 65, 66, 84-88, 92-94, 111-113, 115]

PEA: THE CLINICAL PERSPECTIVE

Clinical research on PEA started in the 1960s and 1970s, especially in the Czech Republic. [117-121] PEA, at that time under the brandname 'Impulsin' was indicated for prevention of flu and respiratory diseases and immune system enhancement. Many years have since passed, with PEA being subsequently explored in a variety of pain states: diabetic neuropathy, carpal tunnel syndrome, dental and temporomandibular joint pain, arthritic, postherpetic and chemotherapy-induced neuropathic pain. Below we will describe data from a number of human clinical pain trials. The main results are outlined in Table **1** and have been discussed by Keppel Hesselink. [122] Overall, more than 2000 patients have been successfully treated with PEA, and no adverse effects reported in any of the trials.

Effect of PEA on Central and Peripheral Neuropathic Pain

A key dosing trial was performed in Italy by Guida and colleagues. [123] These authors carried out a placebo-controlled, double-blind, randomized study on 636 patients suffering from lumbosciatic pain (hernia and nerve root compression), with a mean Visual Analogue Pain Scale

Table 1. Analgesic Effect of PEA on Chronic Pain: Overview of Clinical Trials.

	Indication & *Trial Design*	**Number of Patients**	**PEA Dosage**	**Main Results**	**Ref**
Peripheral Neuropathic Pain	Sciatic pain *Double blind, randomized, two doses of PEA vs placebo*	636	1st arm: 300mg/die x 3 weeks 2nd arm: 300mg/bid for weeks	Significant decrease of pain on VAS (from 7 to 2)	[123]
	Sciatic pain *Double blind, randomized, two doses of PEA vs placebo*	111	1st arm: 300mg/die for 3 weeks 2nd arm: 300mg/bid for weeks	Significant decrease in the duration of treatment with anti-inflammatory and analgesic drugs	[142]
	Pudendal neuralgia *Case Report*	1	300mg/tid gradually decreasing to 300mg/die for1 year	Resolution of chronic pelvic pain	[124]
	Diabetic neuropathic pain *Open*	30	300mg/bid for 60 days	Significant reduction of pain, burning, paraesthesia and numbness	[125]
	Postoperative pain (surgical extraction of impacted lower third molars) *Single-blind, randomized, split-mouth*	30	300mg/bid for 6 days before and 9 days after surgery	Significant reduction in pain intensity	[126]
	TMJ pain caused by osteoarthritis *Double blind randomized vs NSAIDs*	24	300mg at morning + 600mg at evening for7 days; followed by 300mg/bid for 7 days Vs ibupfofen (600 mg/tid for 14 days)	Significant decrease of pain on VAS (from 7 to 0.7) an significant better maximum mouth opening compared to ibuprofen.	[127]
	Diabetic neuropathy pain associated with carpal tunnel syndrome *Group-controlled, randomized, PEA treatment v standard care*	50	600 mg/bid for 60 days	Significant relief of pain. Significant improvement of neurophysiologic parameters	[131]
	Carpal tunnel syndrome in diabetic patients *Group-controlled, randomized vs non-treated patients*	40	600mg/bid for 60 days	Significant reduction of pain and functional status. Significant improvement neurophysiologic parameters	[132]
	Pain associated with carpal tunnel syndrome *Group-controlled, randomized, two doses of PEA vs non-treated patients*	26	1st arm: 300mg/bid for 30 days 2nd arm: 600mg/bid for 30 days	Significant dose-dependent reduction of pain and improvement of neurophysiologic parameters compared with control group.	[133]
	Neuropathic pain *Open*	27	300mg/bid for 3 weeks followed by 300mg/die for 4 weeks	Significant reduction of pain and improvement of electrophysiological parameters	[134]
	Low back pain *Open* (*Combination therapy)*	20	600mg/bid for 30 days + oxycodone (see text for dosage)	Significant decrease of pain on VAS (from 7 to 2.5)	[136]

Table 1. Contd….

	Indication & *Trial Design*	**Number of Patients**	**PEA Dosage**	**Main Results**	**Ref**
	Neuropathic chronic pain (Diabetic neuropathy and postherpetic neuralgia) *Open* (*Combination therapy)*	30	Combination of Pregabalin+PEA 600mg bid for 45 days + pregabalin (see text for dosage)	Significant decrease of pain on VAS, from 7.6 to 1.8	[137]
	Various pain states (see text) *Open* (*Combination therapy)*	517	600mg/bid for 3 weeks followed by 600mg/die for 4 weeks + Pregabalin and oxycodone (see text)	61% decrease of mean pain score on Numeric Rating Scale	[138]
	Low back pain *Open* (*Combination therapy) Controlled (PEA +standard analgesics group vs standard analgesics only)*	81	600mg/bid for 3 weeks followed by 600mg/die for 4 weeks +/- Standard analgesics (see text)	Significant reduction of pain intensity in the PEA group compared to control group	[139]
	Diabetic neuropathic pain *Group- controlled: Combination of PEA +Pregabalin vs Pregabalin*	74	600mg/bid for 10 days followed by 600mg/die for 20 days followed by 300mg/die for 30 days	Significantly higher rate of responders (i.e., <60% decrease in pain score) in the combination therapy group compared to pregabalin only group.	[140]
	Sciatic pain *Group-controlled, randomized, combination of PEA +standard analgesic therapies vs standard analgesic therapies*	85	300mg/bid for 30 days	Significant relief of pain (scored both on VAS and Oswestry Low Back Pain Scale) in the PEA group compared to the analgesic-only group.	[141]
Central Neuropathic Pain	Neuropathic pain and spasticity in post-stroke patients *Open, controlled PEA + Physiother() vs group treated with only Physiother)*	20	600mg/bid for 60 days followed by 600mg/die for 30 days	Significant decrease of pain and spasticity	[128]
	Neuropathic pain associated with multiple sclerosis *Open*	20	300mg/bid for 60 days	Significant decrease of neuropathic pain	[129]
Chronic Pelvic Pain	Chronic pelvic pain associated with endometriosis/ dysmenorrhoea /interstitial cystitis *Open*	25	200mg/tid (+polydatin 20mg/tid) for 40 days	Significant reduction of pain on VAS (from 6.8 to 1.7). Significant decrease in the use of NSAIDs.	[143]
	Adolescent primary dysmenorrhoea *Open*	20	400mg/bid (+ polydatin 40mg/bid) for 6 months	70% decrease of pelvic pain	[144]
	Chronic pelvic pain and dyspareunia associated with endometriosis *Open (case series)*	4	200mg/bid (+ polydatin 20mg/bid) for 3 months	Significant decrease of pelvic pain. Significant decrease of dyspareunia. Significant reduction in the use of analgesics.	[145]

Table 1. Contd….

	Indication & *Trial Design*	**Number of Patients**	**PEA Dosage**	**Main Results**	**Ref**
	Chronic pelvic pain associated with endometriosis *Double blind, ,randomized paral-lel-group, placebo-controlled*	61	400mg/tid (+ 40mg/tid polydatin) for 3 months Vs celecoxib 200 mg/bid for 7 consecutive days	Significant decrease of cronic pelvic pain, dysmenorrhoea and dyspare-unia in the PEA group compared to placebo group	[146]

Abbreviations: bid, *bis in die* = twice daily; *die*, daily; NSAIDs, non-steroidal anti-inflammatory drugs; tid, *ter in die* = three times daily; TMJ, temporomandibular joint; VAS, visual analogue pain scale..

(VAS) pain score at baseline of 6.5. The study consisted of three arms: placebo, PEA 300 mg/day and PEA 600 mg/day. The results after 3 weeks of treatment: placebo, decrease of pain from mean VAS 6.5 to mean VAS 4.5; 300 mg PEA, 6.5 to 3. 5; 600 mg PEA, 7.1 to VAS 2.1. PEA at the lower dose (300 mg) was significantly better compared to placebo, and higher dose PEA (600 mg) was significantly better compared both to the lower dose and to placebo. No relevant adverse events were reported. In the Youtube and Prezi added to this paper, further details on study outcome are presented and discussed.

Interestingly, a case report on a 40-year-old healthy man with pudendal neuralgia (probably secondary to nerve compression) was recently published. The patient, who originally rated his pain at 8 on the 0–10 VAS, experienced a significant improvement of neuralgia and associated symptoms on PEA, up to 900 mg/day. [124]

The results of an open study performed on 30 patients suffering from diabetic neuropathy were recently presented at the 2011 Congress of the European Shock Society. [125] Orally administered PEA (300 mg/twice daily for 60 days) significantly reduced the clinical sensory symptoms ($p<0.001$), as scored by the Michigan Neuropathy Screening Instrument, Total Symptom Score, and Neuropathic Pain Symptom Inventory. In particular, PEA treatment significantly reduced the severity and frequency of pain, burning, paraesthesia and numbness. Moreover, the study clearly demonstrated that the analgesic effect manifested itself as early as 30 days after treatment start, progressively increased over time and was maintained 1 month after treatment discontinuation [125].

PEA reduced pain after surgical extraction of impacted lower third molars. A randomized, split-mouth, single-blind study was conducted on 30 patients between 18 and 30 years of age requiring lower third molar extraction. Patients underwent bilateral extractions in a randomized sequence, with one extraction being performed under PEA treatment (300 mg/twice daily for 15 days). Perceived postoperative pain, as measured on VAS, was significantly lower with PEA treatment compared to control ($p<0.05$) [126].

PEA was beneficial in osteoarthritic (OA) pain (which is considered a mixed pain, i.e., nociceptive and neuropathic components together) where it performed significantly better than a classical non-steroidal anti-inflammatory drug. In this study a double-blind, randomized group-controlled trial was performed on 24 patients suffering from temporomandibular joint OA and divided in two groups: one (n=12) treated with PEA (300 mg in the morning plus 600 mg in the evening for 7 days, followed by 300 mg/twice daily for 7 more days); the second (n=12) received ibuprofen (600 mg/three times daily for two weeks). Spontaneous pain (on VAS) and maximum mouth opening were recorded and both resulted significantly better in the PEA-treated group compared to the ibuprofen-group [127].

Twenty post-stroke patients, suffering from pain and limb spasticity (i.e., hemiparesis, hemiplagia, paraparesis) received either rehabilitation alone, or rehabilitation therapy and PEA (600 mg/twice daily for 8 weeks, followed by 600 mg/sid for 4 adjunctive weeks). The results of this blind, randomized, group-controlled study revealed that PEA treatment not only reduced pain intensity (as measured by means of VAS) but also decreased spasticity as measured by a modified Ashworth scale. The difference between the two treatment groups were statistically significant ($p<0.0006$). No side effects were reported [128].

A further study on the effect of PEA on central neuropathic pain was performed on 20 patients (age 38-75 yrs) suffering from MS and presenting neuropathic pain of the lower limbs, characterized by dysaesthesia along with allodynia, paraesthesia, cramping pain and burning feet. Pain severity was evaluated by means VAS and was significantly reduced in14 out of 20 patients ($p=0.001$) after 2 month-treatment with PEA 600mg/day [129].

Lastly, it is interesting to note that in an open observational study, performed on 8 patients with facial postherpetic neuralgia, a topical preparation containing PEA (twice daily applications to the affected site for two to four weeks) successfully controlled postherpetic pain. Five patients (62.5 %) experienced a mean pain reduction on VAS of 87.8 %. The therapy was well-tolerated by all patients, with no unpleasant sensations or adverse events [130].

Effect of PEA on Electrophysiologic Changes in neuropathic Patients

In addition to clinical signs (i.e., pain, spasticity) also electrophysiologic deficits improved under PEA treatment. A group-controlled, randomized study was performed in 50 diabetic patients suffering from carpal tunnel syndrome with moderate pain [131]. The control group (standard care, n=25) was tested against PEA (600 mg/twice daily, n=25). A

significant improvement in pain at endpoint in the PEA-treated group compared to the control group was noted ($p < 0.0001$). Moreover, the neurophysiologic parameters assessed (sensory conduction velocity and nerve distal motor latency) improved with PEA treatment. No relevant side-effects were documented.

In a more recent study from the same group [132], 40 diabetic patients with mild-to-moderate carpal tunnel syndrome were treated orally with PEA (600 mg/twice daily for 2 months). These patients presented a significantly decreased pain severity, self-reported symptom severity and functional status (the Boston Carpal Tunnel Questionnaire) and electrophysiologic parameters, as early as 1 month after the beginning of PEA treatment.

A further randomized, group-controlled study on patients with carpal tunnel syndrome and clear neurophysiologic abnormalities and pain was performed with a three-arm design: control (no treatment during the study period, n=12), PEA (300 mg/twice daily, n=6), PEA 300 mg/four times daily (n=8). There was a significant improvement in neurophysiologic parameters (distal motor latency) in both dose arms, with the higher dose being more effective [133]. Further, there was a clinically relevant decrease in pain and fewer signs of Tinel in treatment groups 30 days on. No relevant side-effects were noted [133].

In a preliminary open study on 27 patients with painful neuropathy who were either drug naïve or non-responders to other drugs, PEA (300mg/twice daily for 3 weeks, followed by 300mg/daily for 4 weeks) appeared improve nerve function and reduce neuropathic pain. In this study pain was evaluated on an 11-point numerical rating scale, while nerve function was assessed by nerve conduction (for non-nociceptive fibres) or laser evoked potentials (for nociceptive fibres). PEA treatment increased the amplitude of sural and ulnar sensory nerve action potentials, and decreased the mean pain score. After treatment, the sensory index (i.e., the mean value of the afferent pathway-related neural responses) was higher compared to that at baseline. All results reached statistical significance ($p<0.05$) [134].

Finally, this same group of investigators assessed the effect of PEA on pain and nerve function in patients with chemotherapy-induced painful neuropathy [135]. Twenty patients underwent thalidomide (50-200 mg daily) and bortezomib (1.3 mg/m2 twice a week) treatment for Kahler's disease (multiple myeloma). Chemotherapeutic agent-induced neurotoxicity, evidenced as neuropathic pain development and nerve function decline, occurred during the first 3 months. Treatment with PEA (300 mg/twice daily) was carried out between months 3-5. Patients entering the study all suffered from neuropathic pain, and scored at least 4 on Bouhassira's DN4 screening tool for neuropathic pain. All patients were evaluated before and after the two-month treatment with PEA. Parameters measured by blinded observers were: (i) pain and warmth thresholds; (ii) motor and sensory nerve fibre function; (iii) laser-evoked potentials.

Nerve conduction studies consisted of sensory nerve action potentials from sural and ulnar nerves, as well as compound motor action potentials from peroneal and ulnar nerves.

Pain as measured on the VAS decreased from 4.5 ± 1.2 to 3.4 ± 1.0. All neurophysiologic measures-assessing Aα, Aβ, and Aδ fibre functionality significantly improved compared to baseline, while all patient continued their bortezomib/thalidomide therapy ($P < 0.05$). None of the variables, however, returned to normal. Had the patients not been treated, nerve function would have deteriorated further and pain increased, making it necessary to stop or reduce chemotherapy.

Although a placebo effect might play a role in the reduction of pain-intensity, the changes in neurophysiologic measures indicate that PEA exerted a neuroprotective effect on myelinated nerve fibers. Without dose-reduction of chemotherapy one would not expect an improvement between months 3 and 5. On the contrary, further deterioration would be expected.[135] The authors concluded: " PEA, possibly by moderating mast cell hyperactivity, relieved conduction blocks secondary to endoneural edema. In a severe condition such as painful neuropathy associated with multiple myeloma and chemotherapy, a safe substance such as PEA provides significant restoration of nerve function"[135].

PEA May Synergize with Classical Analgesic Drugs

A number of clinical trials have described a synergistic action between PEA and other analgesics, e.g. opiates and antiepileptic drugs used for neuropathic pain. The first example is the report by Desio, [136] who conducted an open study in 20 patients suffering from chronic pain and unresponsive to a variety of analgesics. In particular, patients suffered from low back pain secondary to collapsed vertebrae, lumbar spinal stenosis syndrome and slipped discs. Treatment regime was as follows: oxycodone daily (5 mg) for 5 days, followed by 5 mg/twice daily for 25 days; in addition, PEA (600 mg) was given twice daily for 30 days. Pain score decreased from a mean of VAS 7 at entry to mean VAS 2.5 at day 30 ($p<0.001$). Moreover, pain was observed to decrease as early as the 10^{th} day of treatment, and was maximally reduced at the end of treatment (day 30). No adverse events and no drug-drug interactions were observed.

In a further trial by the same author, PEA was successfully associated to pregabalin in a 45-day treatment of 30 patients suffering from chronic pain due to diabetic neuropathy or postherpetic neuralgia. [137] The treatment regimen was as follows: PEA (600 mg/twice daily) for the whole study duration, associated with pregabalin 75 mg/twice daily for 10 days, followed by a daily dose of 75 mg in the morning plus 150 mg in the evening for the next 10 days; then 150 mg/twice daily for a further 10 days, and finally 200 mg/twice daily for the remaining 15 days. The severity of pain, as measured using VAS, significantly decreased during the duration of the study (45 days), from 7.9 to 1.8 ($p<0.0001$).

A preliminary report on chronic pain due to different conditions also showed that patients benefited from PEA as an adjunct to classical analgesic drugs. The study was performed on 517 patients, suffering from radiculopathy and/or osteoarthritis (64.6%), failed back surgery syndrome (12.77%), postherpetic neuralgia (5.8%), diabetic neuropathy (4.64%), oncologic pain (3.29%), or other pain states (e.g., trigeminal neuralgia, post-traumatic neuropathy; 8.9%). PEA (600 mg/twice daily for 21 days followed by 600 mg/day for

a further 30 days) was added to a fixed dose of pregabalin and oxycodone hydrochloride. Pain was scored at the beginning and end of treatment (51 days) by means of a Numeric Rating Scale. A 61.1% mean decrease of pain was recorded [138].

The efficacy of PEA as part of a multimodal analgesic therapy in patients with low back pain was presented at the Naples Pain Conference in 2010 [139]. Eighty-one patients were divided in two groups: the first group (n=41) received PEA (600 mg/twice daily for 21 days followed by 600 mg/day for the remaining 30 days) on top of standard analgesics (pregabalin, gabapentin, amitriptyline, duloxetine); the second group received standard analgesics only. At day 51 (endpoint) PEA-treated patients had less pain compared to standard care ($p<0.05$). No side effects or drug-drug interactions were observed.

More recently, data on the synergism of PEA combined with pregabalin were presented at the 34th AISD Congress by Adiletta and coworkers [140]. The authors performed an open study on 74 patients suffering from diabetic neuropathic pain divided in two groups: pregabalin monotherapy (titrated up to 600 mg/day) or pregabalin with added PEA at a decreasing dose from 600 mg/twice daily to 300 mg/day. Pain severity was evaluated by means of Brief Pain Inventory; the response to treatment was considered to be at least a 60% decrease in pain score. There was a significantly higher rate of response to pregabalin plus PEA compared to pregabalin only (73% responders versus 40%) $p<0.01$. No side effects or interactions were observed. [140]

In a group-controlled, randomized study performed on 85 patients suffering from lumbosciatic pain, a 30-day treatment associating PEA (600 mg/day) to standard analgesic therapy was statistically better in relieving pain than the same duration treatment with analgesics alone. This was true for pain evaluations with either VAS or the Oswestry Low Back Pain Scale [141].

Lastly, a randomized, double-blind study, performed using the same design and dose regimen as Guida and collaborators [123] showed a statistically significant decrease ($p<0.05$) in the duration of treatment with anti-inflammatory and/or analgesic drugs in the PEA-treated group compared to the placebo group [142].

Overall, these results suggest that PEA may exert a sparing effect on drugs classically used in chronic pain management.

Effect of PEA on Visceral Pain

The results presented so far clearly illustrate that PEA benefits somatic pain, from neuropathic to postoperative and mixed pain. Interestingly, also chronic pelvic pain, i.e. visceral pain, has been shown to respond to PEA. In particular, when combined with polydatin (i.e. the natural glucoside of resveratrol with anti-inflammatory and antioxidant effects), in the ratio 10:1, PEA exerted an important relief of pelvic pain.

In an open study of 25 female patients suffering from endometriosis (n=15), interstitial cystitis (n=6) and dysmenorrhea (n=4) a 60 day-treatment with PEA (200 mg/3 times a day) plus polydatin (20 mg/3 times a day) resulted in a significant decrease of pain, with a VAS score reduction from 6.8 (before treatment) to 3.2 (after 30 days) and 1.7 (after 60 days - study end). Moreover, the combined use of non-steroidal anti-inflammatory drugs significantly decreased [143].

A further preliminary study on the effect of PEA on dysmenorrhea was presented at the Pediatric and Adolescent Gynecology Congress 2010 [144]. Twenty adolescent girls were found to benefit from PEA + polydatin treatment, with a 70% reduction of dysmenorrhea after a 6-month treatment (PEA 200 mg + polydatin 20 mg/3 times a day).

A case series on chronic pelvic pain successfully treated with PEA was recently published. Four patients presenting a endometriosis-related pain intensity >5 on VAS were enrolled and monitored during 3 months of the following treatment: oral PEA (200 mg) and polydatin (20 mg), twice daily for 90 days. Chronic pelvic pain intensity due to endometriosis and deep dyspareunia, dyschezia, dysuria or dysmenorrhoea was evaluated on VAS at baseline and during the programmed follow-up after 1, 2 and 3 months of treatment. All patients experienced pain relief as early as 1 month after starting treatment ($p < 0.0069$). For dyspareunia there was a significant reduction at day 30, which remained constant until the end of the study ($p < 0.0132$). The reduction in pain intensity was paralleled by a statistically significant ($p < 0.0176$) reduction in analgesics use [145].

In a randomized, double-blind, parallel-group, placebo-controlled clinical trial on 61subjects with endometriosis, patients were submitted to a first line laparoscopic conservative surgery and randomized into 3 groups: group A (n = 21) PEA (400 mg) +polydatin (40 mg) twice daily for 3 months; group B (n = 20)placebo for 3 months; group C (n = 20) a single course of Celecoxib 200 mg twice daily for 7 consecutive days. A marked decrease in dysmenorrhoea, dyspareunia and pelvic pain was observed, with the combination of PEA and polydatin significantly more effective than placebo ($p < 0.001$). The authors stated that "this safe association shows an optimal control of pain and could be used in patients who are unable to receive other therapies" [146].

DOSE RECOMMENDATIONS OF PEA

The results of clinical trials with PEA in human pain states, together with current preclinical data suggest that PEA might possess neuro-regenerative properties [147]. PEA is available for clinical use and is marketed by the Italian company Epitech under the trade name Normast® (for neuropathic pain) and Pelvilen® (for pelvic pain) [52]. Two different formulations have been developed, an ultramicronized formulation of PEA for sublingual use, containing 600 mg, and tablets of 300 or 600 mg PEA. Combination of PEA with opioids, gabapentoids and antidepressants for treating chronic and neuropathic pain is possible, and no drug-drug interactions have been reported. [148] Synergistic effects of PEA with pregabaline and oxycodone have been described, as discussed above. [136-142]

Based on our knowledge to date, recommended starting treatment dose for PEA is: twice daily 600 mg ultramicronized PEA, in 600 mg sublingual sachets, 10 days or, in the case of central neuropathic pain 20-30 days. After the initial loading dose phase, patients can be treated with 600 mg tablets twice daily. If pain is reduced at least 30-50%, a lower dose can be selected, i.e., 300 mg/twice daily. In the

case of a relapse under tablet regime, transfer patients to 600 mg Normast sublingual sachets for at least 20 days. Some patients, especially those with central neuropathic pain may respond better to sublingual sachets, but relapse on tablets.

Physicians wishing to consult the author can do so by sending an email to: jan@neuropathie.nu

An English presentation on this topic for Italian pain specialists, presented at the 2011 congress of 'La società italiana di anestesia analgesia rianimazione e terapia intensiva (SIAARTI) can be found (following a 1.5 minute introduction in Italian) on: http://www.youtube.com/watch?v=3wgdwcijCt0

Illustration for this article as a Prezi:

http://prezi.com/zgzjdoudele-/glia-modulator-is-breakthrough-in-treatment-chronic-and-neuropathic-pain/

CONFLICT OF INTEREST

None declared.

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