REVIEW

Practical update on oral palmythopylethanolamid (PEAum) in the management of chronic pain. Narrative review

ABSTRACT:

Introduction: Chronic pain is a cause of great suffering for patients and their relatives and one of the most relevant health issues. Available treatments, generally based on analgesic drugs, mainly NSAIDs, and others, including opioids, achieve a partial and frequently temporary relief, with a large number of potential adverse effects.

Development: New investigation lines of research in this field are looking to develop safe analgesics like ultramicronised palmitoylethanolamid (um-PEA), a nutritional oral supplementation administered at a dose of 600 mg/12-24 hours, to counteract neuroinflammation, slow down pain chronicity, enhancing the antinociceptive effects of analgesic drugs.

Conclusions: PEAum is a nutritional support showing analgesic, anti-inflammatory and nerve regenerative properties, indicated for use in case of chronic pain, specially neuropathic pain. Um-PEA is able to decrease pain preventing, partially, central sensitisation. Um-PEA safety profile and good tolerability represent an additional tool in the management of chronic pain.

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RESUMEN:

Introducción: El dolor crónico es causa de gran sufrimiento para los pacientes y familiares y uno de los problemas relevantes de salud. Los tratamientos actuales, mayoritariamente a base de fármacos antinflamatorios y otros analgésicos, incluidos los opioides, consiguen un alivio parcial y muchas veces temporal, sumándose un gran número potencial de efectos adversos.

Desarrollo: Las nuevas líneas de investigación en este campo tratan de desarrollar sustancias más inocuas y que ayuden en el alivio del dolor. Una de ellas es la palmitoiletanolamida ultramicronizada (PEAum), comercializada como producto nutricional, a dosis de 600 mg/12-24 horas que, administrada por vía oral, incide sobre la neuroinflamación, ralentizando la cronificación del dolor y potenciando los analgésicos, y a su vez reduciendo su consumo.

Conclusiones: PEAum es un producto nutricional, con características analgésicas, antinflamatorias y regeneradoras nerviosas. PEAum está indicada en cuadros de dolor crónico, y sobre todo neuropático, como neuroprotector, reduciendo el dolor y evitando en parte la sensibilización central. La facilidad de manejo de la PEAum, seguridad y buena tolerabilidad la sitúan como un producto que aporta un valor añadido frente al dolor crónico.

Introduction

Chronic pain represents one of the main public health problems in the 21st century, in terms of suffering for the patient and their relatives, as well as costs for the healthcare system. Its high prevalence (around 20%), problematic and complexity entails a great deal of research into its pathophysiology and, of course, its treatment approach, both from a pharmacological and non-drug point of view (1). Research on analgesic medication is usually focused on the discovery of new drugs, or the use of already known compounds but with new therapeutic possibilities.

One of the most striking varieties of chronic pain is the one related to neuropathic pain (NP), defined as pain caused by a lesion of the somatosensory system, both at the peripheral and central nervous system level. It is characterised by the possibility of occurring in more than 100 different diseases, involves different pathophysiological mechanisms (not all of them known) and is particularly difficult to treat. One of the processes involved in NP is neuroinflammation, which could be related to microglia, a cell population from the bone marrow, more frequent and smaller than neurons, that is found in all nervous tissue. These cells are activated and proliferate in inflammatory processes of the nervous system and when chronic pain appears, especially NP (2). Other glial cells involved in these processes, albeit to a lesser extent, are astrocytes and oligodendrocytes. Neuroinflammation, associated with endoneural oedema, angiogenesis and microvascular alterations at neuronal level, has been one of the most studied pathophysiological concepts in the last 20 years because of its involvement in the development of NP and pain chronification. Its participation in the central sensitisation of pain has been a determining factor in understanding how this pain becomes chronic. Moreover, several studies have opened up new therapeutic possibilities and new lines of research in this field. In fact, inhibitors of microglial activation at experimental level are known to reduce both hyperalgesia and allodynia (present in different clinical profiles of neurological damage) and could be used as new products against chronic pain, mainly NP (2-4).

Classic anti-neuropathic medication includes anticonvulsants, antidepressants, opioids in severe pain, and other drugs (ketamine, baclofen, capsaicin...). Despite the large number of
drugs against NP available, the relief obtained hardly exceeds 50 % or 60 % and in most cases at the cost of various significant adverse effects. Hence, it seems clear that new lines of research on analgesic are needed, especially at a time of opioid crisis, to provide analgesia with fewer adverse effects. Moreover, these new approaches should be based on other targets and underlying mechanisms of pain, such as neuroinflammation.

Lately, diet, nutrition and nutritional support with substances, some of them endogenous, are becoming increasingly relevant in the field of chronic pain, both in non-oncological and oncological pain. Many articles published in recent years show that this represents one of the growing areas of study (5,6). The relationship between overweight, obesity and increased likelihood of chronic pain is well known. Similarly, dietary modifications have been studied in a pain unit as a factor related to chronic pain (7). A meta-analysis carried out in 2018, and other subsequent studies, concluded that certain dietary modifications, or the addition of nutritional support to the diet, would reduce pain in certain situations of chronic pain (5,7). Among the main objectives of research with nutritional support and dietary modifications is to reduce the inflammatory component of pain, trying to relate it to neuroinflammation, a factor favouring central sensitisation and pain chronification (8).

In the same vein, another line of research tries to understand how diet and nutrients influence the intestinal microbiota, which seems directly related to the regulation of neuroinflammation (9). Furthermore, it has been shown that different nutrients activate the microglia, favouring the process of neuroinflammation and pain chronification, and others reduce or prevent it (10).

Some of the most studied molecules with the potential to act on neuroinflammation have been the autacoids or Allia-amides and above all palmitoylethanolamide (PEA), an endogenous substance. The most recent findings on PEA suggest that it may act on some of the channels, receptors and neurotransmitters involved in neuroinflammation and the triggering of NP. In the 1990s, Nobel laureate Rita Levi-Montalcini drew attention to the power of PEA as a potent anti-inflammatory and antinociceptive, which has since been endorsed by other researchers (11,12). Subsequently, its neuroprotective power was evinced, regulating mast cells and neuroglia, and it was shown how animals with chronic pain, in turn, had reduced levels of PEA (13). This molecule new properties, indications and applications in medicine have been partly due to its new formulations, such as ultramicronised PEA (um-PEA). Research over the last 10 years has focused on the important treatment possibilities of um-PEA in different pain syndromes with a high neuropathic component (14).

The main objective of this narrative review is to provide an update on a nutritional product such as PEA, to show both its mechanisms of action, which have been largely investigated in recent years, and the results obtained in animal and clinical models of chronic pain and inflammation. For this purpose, we have used different databases such as PubMed, Scielo and Medline, selecting those articles with the greatest relevance and impact.

**PEA pharmacology**

PEA (generic = Palmidrol) corresponds to the chemical name (IUPAC): N-(2-hydroxyethyl) hexadecanamide; CAS Number: 544-31-0. It has the molecular formula: C_{18}H_{37}NO_{2} and has a molecular weight of 299.5 (Figure 1). It is a naturally occurring lipid compound that was first identified in soy-lecithin, egg yolk, or peanut flour in the 1950s (15,16), and later in mammalian tissues. PEA belongs to the family of N-acyl-ethanolamines (NAEs), endogenous biologically active endocannabinoid-like lipids, to which anandamide (AEA) and oleylethanolamide (OEA) belong (17). It is synthesized in the lipid bilayer on demand, acts locally, and is found in all tissues, including the brain. PEA is thought to be synthesized as a pro-homeostatic protective response to some cellular injury.

Currently, it can be found as a nutritional product in Spain and is commercialised under the name of Normast® (18,19).

**Pharmacokinetics**

PEA is a highly lipophilic compound and hence the difficulty to elaborate a dosage form that is optimally absorbed, since it is practically insoluble in water (20). Therefore, for its formulation, micronisation has been used to increase the surface area and thus facilitate dissolution, a process prior to and necessary for absorption. Once absorbed, when administered orally, pre-syste-
mic metabolism or the hepatic first-pass effect must also be taken into account, as this is a phenomenon that can reduce bioavailability. The bioavailability of the different presentations of PEA is not known, nor is its inter-individual variability. However, the micronised and ultra-micronised forms seem to show at least sufficient absorption and bioavailability, as demonstrated by their efficacy in animals (21,22) and humans (23). This fact has led to a number of investigations to evaluate their potential application as a drug for different types of diseases (24). Micronised and ultra-micronised PEA have demonstrated faster dissolution and absorption rates, better bioavailability and pharmacokinetics and superior efficacy compared to the original form, which has a larger and more variable particle size (25,26). In addition to micronisation, other dosage forms that improve the bioavailability of PEA have been tested, such as the LipiSperse® system. In the latter case, the addition of surfactants to a lipophilic molecule such as PEA, with a high particle size (>100 microns), does not seem to favour an effective and prolonged dispersion of the active substance in the aqueous phase. Further studies are undoubtedly necessary to confirm the advantage in bioavailability of the LipiSperse® system over the use of non-micronised PEA.

On the other hand, the appearance of twin plasma peaks after a single administration of PEA indicates the existence of an enterohepatic cycle (27). Enzymes that hydrolyse PEA are found, among other organs and tissues, in the intestine and liver (28). In an attempt to avoid the first-pass effect, administration of PEA in the form of prodrugs (2-palmitoylaminoethyl L-valinate hydrochloride) has been investigated, and although it did not undergo hepatic hydrolysis, it presented worst bioavailability than PEA (29).

To measure the incorporation of PEA into the blood, a dose of 300 mg of micronised PEA was administered to humans. Plasma concentrations after two hours were twice as high as before administration, returning to baseline values at 4 and 6 hours (30).

As the absolute bioavailability of the various dosage forms of PEA has not been quantified, it is not possible to calculate its apparent volume of distribution, although approximations have been made in animal studies. In a study in rats, the distribution of PEA has been measured using an oral dose of tritium-labelled PEA, showing distribution to the brain, particularly to the hypothalamus. Furthermore, a significant accumulation in the pituitary gland and adrenal glands has been observed (31).

Since the main receptor for PEA, peroxisome proliferator-activated receptor α (PPAR-α), is intracellular, this molecule needs to cross the cell membrane to access the cytoplasm and interact with peroxisomes. This has been demonstrated using labelled PEA ([1-14C] PEA) and C1300 N18 neuroblastoma cells (32).

PEA, being an ester, is metabolised by hydrolysis in a Phase I reaction, forming two metabolites, palmitic acid and ethanolamine. Two enzymes are known to catalyse this reaction, FAAH (Fatty Acid Amide Hydrolase) in rat liver and FAAH-2 in humans (33). These enzymes play an essential role in the catabolism of exogenously administered PEA, and other fatty acid amides such as AEA and oleylethylamide (34,35).

Metabolism of palmitic acid and the metabolic pathway of PEA are well understood:

- PEA palmitic → acid → incorporation into phospholipids

But the rate at which orally or topically administered PEA is hydrolysed to palmitic acid before excretion, via renal or other routes, is not known (36).

**Pharmacotherapy**

In a targeted Pubmed search using the words “Palmitoylethanolamide & chronic pain” and the filters “Clinical and Human Trials”, multiple publications appear regarding the clinical use of PEA in chronic pain. First article was published in 2007, and on the other hand, several authors have recently carried out systematic reviews on the use of PEA in humans to treat or prevent chronic pain of different aetiologies, some of them very recent and of high quality (20).

In the most recent review (37), the authors have carried out a meta-analysis in which, after reviewing the efficacy and safety
of PEA in different indications, they conclude, among other statements, “that clinical research is needed to strengthen the evidence in this regard, and emphasise the promising results obtained in the reduction of rescue medication in the treatment of poly-medicated elderly patients with chronic pain”. This information deserves special attention in clinical research on PEA, as it could reduce the dose of analgesics administered to the patients, thus minimising their side effects. These unwanted effects could be even avoided in almost half of the patients, thus preventing their admission to geriatric units (38). This is of the utmost importance for poly-medicated elderly patients, due to comorbidities (39) and is related to inappropriate prescriptions (40). Indeed, according to the Italian Silver Network Home Care project, 49% of geriatric patients suffer from daily pain being treated with level I analgesics, and according to the World Health Organisation (WHO) only 25% of cases receive treatment. The latter also refers to medicinal plant-drug interactions, which occur in elderly patients and which have been less investigated (41). It seems obvious that there is a need for clinical research evaluating the efficacy and safety of adjunctive treatment with PEA to reduce the need for rescue medication. The studies conducted should be designed with an adequate sample size, based on calculations according to current literature and include elderly patients suffering from musculoskeletal, neuropathic and mixed pain, and they should investigate the simultaneous lowering of doses of analgesics such as coxibs, opioids and gabapentinoids.

With regard to the safety of PEA, it should be noted that it is an endogenous compound whose two metabolites are well known and to date have not shown safety problems, so it was to be expected that PEA would behave throughout its dose spectrum with great safety and a high therapeutic range. Thus, a large number of authors have demonstrated its safety and tolerability in different dosage forms and therapeutic indications (12,17,20,37,42-44).

**Clinical relationship between PEA and nociception**

PEA acts through different analgesic synergistic mechanisms of great relevance in nociceptive transmission through the central and peripheral nervous system, which are being increasingly elucidated. Different analgesic mechanisms are attributed to PEA (12), among them:

- The first analgesic mechanism is related to the anti-inflammatory power of PEA, acting as a regulator of mast cells (45).
- The second mechanism is related to the activation of two receptors:
  a) Activation of the specific receptor PPAR-α, also known as nuclear receptor subfamily 1 - group C - member 1 (NR1C1), an important regulator of lipid metabolism involved in inflammatory processes (46).
  b) Indirect stimulation of PEA on CB1 and CB2 cannabinoid receptors, by inhibiting the degradation of AEA (endocannabinoid), which closely relates to its anti-inflammatory and analgesic effects. Its expression at brain presynaptic and peripheral levels would help control neuroinflammation and have some neuroprotective effect via microglia (48,49). PEA also acts on new cannabinoid receptors, G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 119 (GPR119).
- The third mechanism is based on the “entourage hypothesis” and proposes that the anti-inflammatory and antinociceptive effects of PEA are due in part to potentiation of endocannabinoid and/or vanilloid actions of receptors such as the highly antinociceptive transient receptor potential vanilloid 1 (TRPV1). PEA acting at the TRPV1 receptor induces antidromic release of neuropeptides closely involved in neurogenic inflammation, such as substance P (SP) and calcitonin gene-related peptide (CGRP), and consequently exerts pro-inflammatory effects (12,48).
- A fourth mechanism that could dampen pain would come from the nerve regenerative power of PEA, shown after nerve injury in animals, preventing the onset of NP or reducing its intensity (13,49).

A summary of the main analgesic mechanisms of action attributed to PEA currently known are listed in table I and have recently been reviewed in detail (14,36).
PEA and analgesic efficacy in animal pain models

The first experimental animal studies with PEA were conducted in 1998. Since then, research on PEA has focused on various animal pain models, and a solid and robust scientific basis has been established to support the strong analgesic potential of this substance.

Inflammation

In different animal models of inflammation, prior oral administration of PEA (0.1 to 10 mg/kg) before applying carrageenan or formalin in a dose-dependent manner, caused a reduction in the release of substance P (49,50). Similarly, a curative anti-inflammatory effect could be demonstrated with administration of PEA after inflammation had been generated (49,51).

Conclusion: these findings supported the preventive and curative anti-inflammatory effect of PEA in acute inflammatory models.

Mechanical allodynia

In 2008, it was demonstrated (52) that PEA reduced mechanical allodynia in the constriction injury of the sciatic nerve model in mice.

Conclusion: PEA relieved and modulated NP reducing inflammation, distal oedema and macrophage infiltration of nerve tissue.

Mechanical and thermal hyperalgesia

In the animal model of NP induced by subcutaneous plantar carrageenan injection, PEA reduced both mechanical and thermal hyperalgesia (48). Similarly, a pain reduction was found following plantar formalin injection (50,53). PEA was also shown to be effective in reducing thermal hyperalgesia in animals following intraplantar administration of nerve growth factor (NGF) (50,54). Moreover, in other pain models, as the partial ligation of the sciatic nerve model in rats, intraperitoneal administration of PEA at a dose of 100 mg/kg reduced mechanical hyperalgesia (55). This was endorsed by other authors (52), who demonstrated that PEA reduced both allodynia and hyperalgesia in the same model of NP in rats, and also showed a large reduction in mastocytes, which is interpreted as an anti-inflammatory and neuroprotective effect of PEA. More recently, other authors have endorsed the even greater efficacy of um-PEA in the rat sciatic nerve constriction model, where pain, mechanical allodynia and thermal hyperalgesia were significantly reduced (56).

Conclusion: PEA showed analgesic efficacy on hyperalgesia (another key symptom of NP) in different pain models. This was associated with direct improvement of pain and associated comorbidity.

Induced diabetic neuropathy model (57,58)

Using a diabetic neuropathy-like model induced by injected streptozotocin (Ahlgren’s model) in rodents, where both allodynia and hyperalgesia appeared, it has been demonstrated that micronised and non-micronised PEA reduced nerve damage, neuronal oedema and microglia activation.

Conclusion: the use of PEA led to a reduction of mechanical and thermal hyperalgesia in the induced painful diabetic polynuropathy model, decreasing global hypersensitivity and improving motor activity.

Preclinical model of chemotherapy-induced neuropathy

These authors (59,60) observed that in experimental oxyplatin-induced neuropathy in animals, PEA therapy reduced pain and hyperalgesia, increasing pain threshold. Similarly, other authors used the paclitaxel-induced neuropathy model in mice to demonstrate similar results with the use of PEA.

<table>
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<tr>
<th>Table I - Mechanisms of action related to pain in which PEA is involved (12,14, 17,20,48).</th>
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<tbody>
<tr>
<td>A. Autacoid effect, regulating and antagonising mast cell activation</td>
</tr>
<tr>
<td>B. Activation of two specific receptors: Specific PPAR-α receptor (involved in inflammatory processes) CB1 and CB2 cannabinoid receptors, indirectly activated by inhibiting the degradation of AEA (endocannabinoid)</td>
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<tr>
<td>C. Entourage effect, which would cause also the activation of the vanilloid receptor TRPV1, which has a high antinociceptive potential</td>
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<tr>
<td>D. Poder regenerativo nervioso</td>
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<tr>
<td>All of them lead PEA to behave as an anti-inflammatory, analgesic, anticonvulsant, immunomodulator with a neuroprotective effect</td>
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Conclusion: authors concluded that PEA has an anti-allodynic, analgesic and neuroprotective effect in neuropathy caused by certain cytostatics. These effects can be attributed to the direct action of PEA both on microglia in the spinal cord and at the peripheral level, reducing neuroinflammation.

Model of complex regional pain syndrome (CRPS)

The classic model of CRPS due to tibial fracture in rodents presents with pain, allodynia, oedema and osteoporosis (61). The use of oral micronised PEA 28 days after fracture reduced pain, allodynia and hyperalgesia in these animals.

Conclusion: several of the classic and detrimental symptoms of CRPS improved with um-PEA.

Visceral pain

Further evidence of analgesic efficacy of PEA, including at the visceral level, comes from the use of PEA at doses of 2.5-30 mg/kg in animal models, showing a reduction on visceral hyperreflexia following bladder inflammation induced in rat by nerve growth factor (NGF) injection (62).

Conclusion: PEA analgesia was demonstrated in another model of pain such as visceral pain.

Table II summarises the animal pain models that have experienced improvement with PEA.

<table>
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<th>PEA and analgesic efficacy in human clinical pain models</th>
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<tr>
<td>Neuropathic pain models (12)</td>
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<tr>
<td>- Diabetic polyneuropathy: according to different authors, PEA has shown pain-reducing efficacy in pain due to painful diabetic polyneuropathy. The dose used was 600 mg every 12 hours.</td>
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<tr>
<td>- Lumbosciatica: PEA was also useful in chronic lumbosciatica conditions. Administered in combination with regular analgesics, it enhances analgesia, reduces pain and reduces analgesic consumption. Little effect of analgesics.</td>
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— Others: it acted in the same manner, in models of postherpetic neuralgia, carpal tunnel syndrome or radiculopathies. Dosage ranged from 300 to 600 mg every 12 h.

Conclusion: in the review conducted (12) on PEA in NP models, clinically significant analgesic improvement was found, without differences in response with respect to gender.

Other pain models (63)

— Low back pain: micronised PEA at a dose of 600 mg/12 hours has recently been shown to be of analgesic benefit when combined with other analgesics for a period of 6 months in chronic low back pain. Reduction of pain and analgesic consumption was clinically and statistically significant, and functional improvement was evident after 6 months of treatment. No major adverse effects were reported, except for mild diarrhoea in some cases, and no dyslipaemia was observed (63).

— Fibromyalgia: similarly, oral micronised PEA appears to have been effective in selected cases of fibromyalgia patients. A total of 359 patients included in a study improved their pain as well as their overall quality of life. The good tolerability of PEA makes it a recommended long-term product for fibromyalgia patients (64).

— Migraine: in migraine, micronised PEA administered at a dose of 1,200 mg has shown efficacy in different studies, reducing the frequency, duration and intensity of attacks, whether used as monotherapy or in combination with non-steroidal anti-inflammatory drugs (NSAIDs).
Arthrosis: in various arthritic conditions, PEA has been shown, in several clinical trials, to improve pain, inflammation and joint function when administered in gonarthrosis, thus reducing analgesic consumption.

Meta-analysis of PEA in the treatment of pain (65)
- The authors in this article made a systematic review of all publications on PEA and its use in pain management.
- A total of 10 controlled trials and 786 patients received PEA versus 517 as a control group, who did not.
- Doses ranged from 300 mg to 1,200 mg/day, with the majority at 600 mg/day.
- Most patients experienced pain relief with the use of PEA.
- Overall tolerability was very good, with few adverse effects, except for isolated dyspepsia and a few mild cases of diarrhoea.
- The limitations of the results obtained are due to the heterogeneity of the different clinical profiles, the scarcity of patients recruited in each trial and the relative masking in the different studies.

Long-term oral um-PEA
Most of the long-term studies with PEA support its excellent tolerability, which is increased by um-PEA:
- In 2016, another article was published (66) on a controlled trial in a small group of 29 patients with multiple sclerosis (MS), treated with um-PEA for 12 months at a dose of 600 mg/day. Half of the patients in the study received a combination of PEA and interferon treatment. These patients were observed to have less pain over the entire time than those who did not receive PEA and were treated with interferon alone. In addition, plasma PEA levels rose and neurological complaints were lower in these PEA-treated patients. The tolerability of PEA was very acceptable and even reduced the local discomfort of intramuscular interferon, possibly by decreasing the local inflammatory reaction. Conclusion: PEA presented a maintained reduction of inflammation, along with excellent tolerability.
- Another publication appeared in 2017 (67) on patients with Parkinson's disease treated with 600 mg daily of um-PEA for 12 months. Patients treated with PEA improved neurological symptomatology, both sensory and motor. No patients had adverse effects attributable to PEA.
  Conclusion: Overall neurological improvement, and safety of PEA management in the long term.
- Another application of PEA was demonstrated in a relevant study conducted in 2019 (68) on 359 patients with fibromyalgia, to whom um-PEA was added to their usual treatment. Dosage ranged from 600 mg/8 hours for ten days, 600 mg/12 hours for twenty days and 600 mg/day for 15 months. Patients reduced their pain and improved their overall quality of life with PEA. Only 36 described mild adverse effects, mostly gastrointestinal.
  Conclusion: PEA produced sustained analgesic improvement and excellent tolerability.

Other beneficial effects of PEA (20)
- Antibacterial and antiviral effect.
- Immunomodulation enhancer, with the possibility of using it as an anti-aging agent.
- Neuroprotective in degenerative diseases such as Alzheimer's, Parkinson's disease or acute stroke.
- In major depression, associating PEA with antidepressants.
- Reduction of muscle injury due to exercise, shortening recovery and promoting aerobic metabolism.
- Improvement of restorative sleep and anxiolytic effect, without the adverse effects of classic hypnotics and tranquillisers.

A total of the articles used in the review are shown schematically in Table III.

PEA indications in different pain syndromes
Although the indications described for oral PEA in acute and chronic pain are multiple, the ones approved by the scientific community and supported by the best evidence are restricted to the clinical pictures shown in Table IV. In most ca-
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### Table III. Most relevant articles on PEA.

**Pharmacology and other generalities related to PEA**

- Briske D, Mallard AR, Rao A. Increased Absorption of Palmitoylethanolamide Using a Novel Dispersion Technology System (LipiSperse). Nutraceuticals Food Sci. 2020;5:2-3. DOI: 10.3964/nus.5.2.3

**PEA research in animal pain models**

Conclusions

— Um-PEA is a nutritional product with exceptional characteristics, with antinociceptive and anti-inflammatory effect.

— The already known mechanisms of action and its action in different animal and human pain models, have turned um-PEA into a substance with a great potential not only analgesic, but also neuroprotective.

### Table III. (Cont.) Most relevant articles on PEA.

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<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Journal and Year</th>
<th>Keywords</th>
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ses, the optimal dose has been 600 mg every 12 hours, at least initially. In any of the indications, it could be used in monotherapy as an alternative to analgesics or in addition to the usual analgesics (Table IV).

### Practical guidelines for the management of PEA in NP

Practical management guidelines are reflected in Table V.
Practical update on oral palmythopylethanolamide (PEAum) in the management of chronic pain. Narrative review

— Um-PEA is indicated in cases of long-standing NP, in monotherapy or in combination with other analgesic drugs, boosting them and reducing their consumption.
— Um-PEA can also be used as neuroprotector, administered beforehand in clinical cases of acute NP, such as neuralgia or radiculopathy, reducing pain and avoiding both central sensitisation and the transition to chronicity.
— Um-PEA’s ease of use, safety and good tolerability make it a product that currently adds value to the analgesic arsenal for chronic pain.

Conflict of interest statement

This article has not been funded in whole or in part by any organisation. The authors declare no conflict of interest.

REFERENCES

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