PEA: A novel anti-neuroinflammatory compound

KEY LEARNINGS

Palmitoylethanolamide

- PEA, or palmitoylethanolamide, is an endogenously produced cannabimimetic compound
- PEA contains analgesic, anti-inflammatory and neuroprotective effects

Mechanisms of action

- PEA exerts its analgesic and anti-inflammatory effects through a broad range of physiological pathways, which include modulation of mast cells, transcription factors, pain sensitisation, cannabinoid receptors, and other endogenous anti-inflammatory and neuroprotective compounds

Neuropathic pain

- Neuropathic pain is one of the most difficult chronic pain conditions to treat
- The compression of nerves induces inflammation within the nerve and nerve root
- PEA's ability to inhibit mast cell migration and activation, and the over-activation of glia and astrocytes, has led to it being extensively studied in neuropathic pain, where it is particularly effective in trapped nerve pain such as sciatica and carpal tunnel syndrome

Further indications

- PEA's anti-inflammatory activity has led to positive results in clinical trials for a broad range of conditions including; osteoarthritis, shingles, peripheral neuropathy, low back pain, fibromyalgia, depression, autism, migraines and cold and flu

Palmitoylethanolamide

PEA, or palmitoylethanolamide, is an endogenously produced cannabimimetic compound[1] that has been extensively studied in clinical and preclinical trials for its analgesic, anti-inflammatory and neuroprotective effects.[2] It belongs to a group of endogenously produced bioactive lipids called N-acylethanolamines (NAEs), which contribute to the regulation of pain and inflammation,[3] and include various cannabinoid receptor ligands and satiety factors. PEA is ubiquitous in mammals, being produced on demand from the lipid bilayer, and was identified as an active anti-inflammatory agent in the 1950s.[4] It is particularly abundant in the central nervous system (CNS), where it is produced by neurons and glial cells, and also in immune cells.[5]

PEA was first isolated from soy lecithin in 1957, however from as early as 1939 it was recognised that feeding dried egg yolk (equivalent to 4–6 eggs) to undernourished children reduced the occurrence of rheumatic fever despite repeated infections with haemolytic streptococcus. This was attributed to an anti-inflammatory component of the yolk, now understood to be PEA.[6]

PEA is found in a number of common foods including cow's milk, breast milk, beans, peas, tomato, alfalfa, corn, soy lecithin and peanuts.[2]

Figure 1: Palmitoylethanolamide

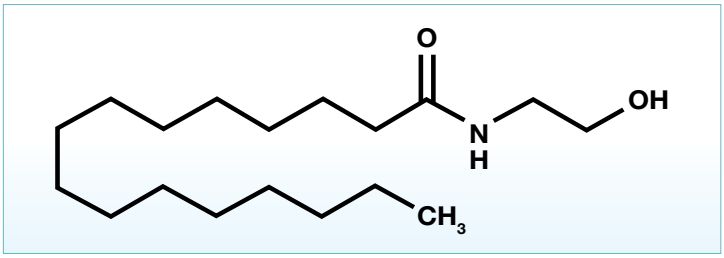

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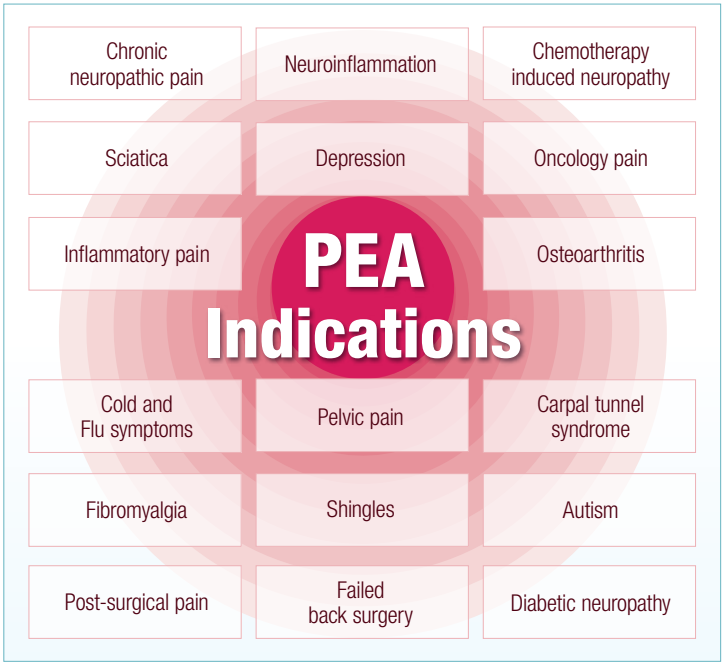
Figure 2: PEA indications



PEA and its known mechanisms of action

Models of chronic inflammation and chronic or neuropathic pain have confirmed the anti-inflammatory and analgesic effects of PEA. Chronic treatment with PEA has been shown in these models to reduce pain and preserve peripheral nerve morphology while reducing endoneural oedema, the recruitment and activation of mast cells, and the production of pro-inflammatory mediators at the site of injury.[7] It has recently been discovered that certain families with inherited pain insensitivity (feel no physical pain) have a polymorphism in the enzyme that breaks down PEA and other amides.[8]

PPAR-α

The primary route by which PEA exerts its effects is through the activation of peroxisome proliferator-activated receptor (PPAR)-α. PPAR-α is a transcription factor that is activated by endogenous fatty acid derivatives including PEA. PPARs control pain and inflammation by switching off the nuclear factor-κB (NF-κB) signalling cascade which leads to the synthesis of proinflammatory mediators.[5] By activating PPAR-α, PEA is also able to stimulate de novo neurosteroid synthesis and may modulate GABA(A) receptors.[5]

Sensitisation

PEA's significant anti-inflammatory effects contribute to the reduction of peripheral and central sensitisation, a type of pain hypersensitivity. Neuronal and non-neuronal cells, including glia and peripheral and central mast cells, mediate this process. PEA is known to regulate the activity of microglial cells and inhibit mast cell activation in both the CNS and periphery, thereby reducing sustained inflammatory nociceptive insults, which contribute to the development of peripheral and central sensitisation.[5]

Figure 3: Molecular target and mechanism of action of PEA. **(A)** PEA can directly activate PPAR-α or **(B)** GPR55. **(C)** PEA through the inhibition of the expression of FAAH, may increase the endogenous levels of AEA and 2-AG, which directly activate CB2 (or CB1) receptors and TRPV1 channels (entourage effect). **(D)** PEA potentiates the activation and desensitisation by AEA and 2-AG of TRPV1 channels (entourage effect). **(E)** PEA may also activate TRPV1 channels via PPAR-α, or increase CB2 receptor expression via PPAR-α.[9]

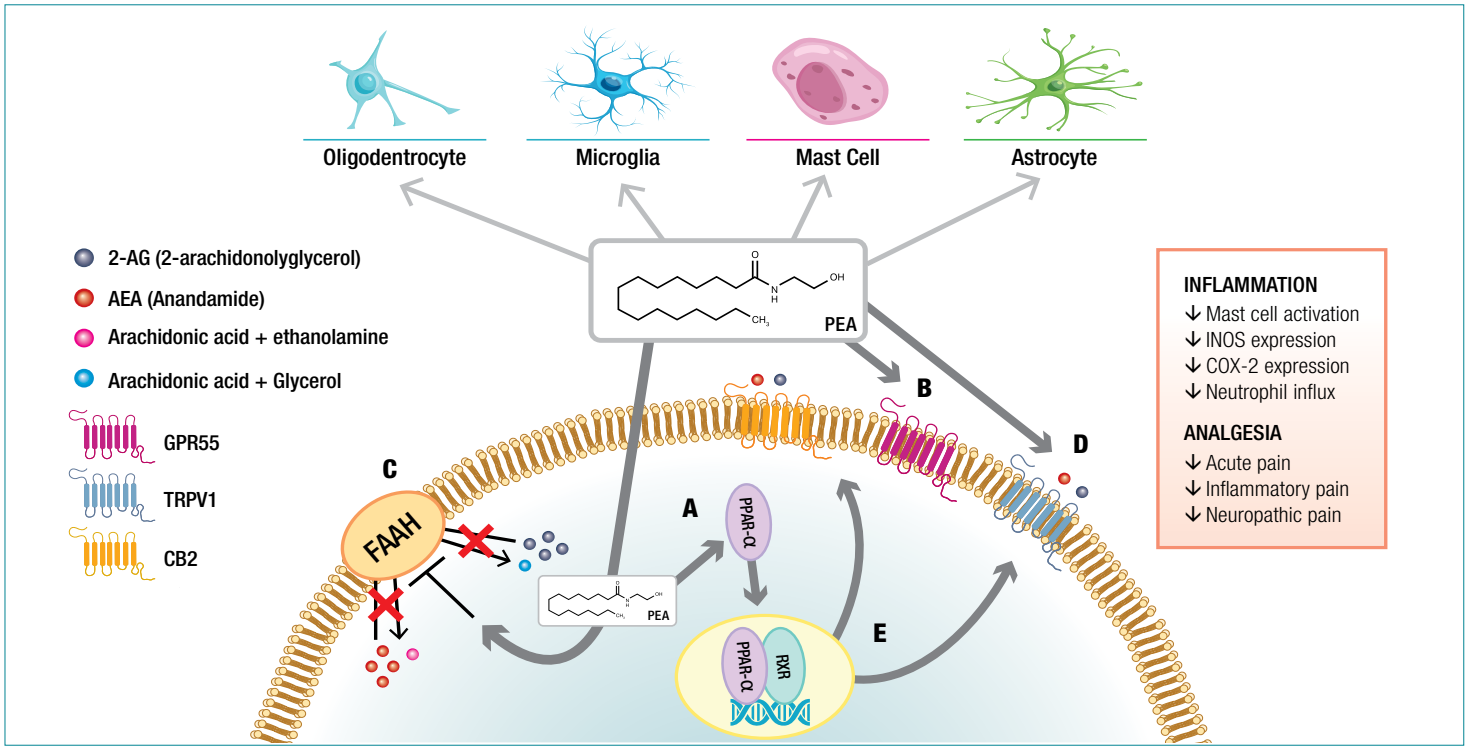
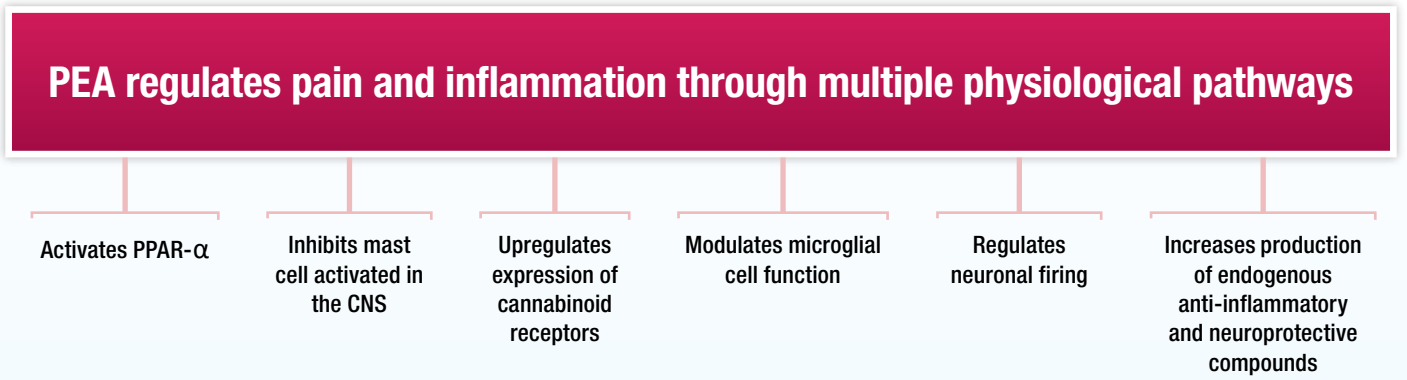


Figure 4: PEA Mechanisms of Action



Microglia and Cannabinoid receptors

Microglia are the primary immune cell in the CNS, and are the first defence against injury or disease of the CNS. The phenotype of the microglia, which is marked by the expression of surface receptors, determines whether an activated microglia will have a cytotoxic, pro-inflammatory effect, or a neuroprotective effect through the reduction of inflammation and by engaging in phagocytosis to remove dying cells, bacteria and myelin debris.[10] Cannabinoid type 2 (CB2) receptors are almost exclusively expressed in glia;[10] selective stimulation of these receptors downregulates microglial reactivity and promotes neuroprotection, promoting analgesia and the release of anti-inflammatory cytokines. While PEA does not have an ability to bind to cannabinoid receptors and is therefore not strictly an endocannabinoid, it has been shown to enhance CB2 receptor expression in microglia by increasing CB2 mRNA and protein expression via a PPAR-α-mediated mechanism.[11]

Mast Cells

Mast cells in the CNS play a significant role in inflammatory and neurodegenerative diseases by sending pro-inflammatory signals to microglia.[5] Additionally, mast cells in the peripheral nerves degranulate at the site of nerve damage, releasing histamine and TNF-α, which sensitise nociceptors and increase recruitment of neutrophils and macrophages.[12] PEA downregulates mast cell recruitment and degranulation.[13] Nerve growth factor (NGF) is a neurotrophic factor released by mast cells, which sensitises and activates nociceptors; PEA has been shown to significantly reduce the release of nerve growth factor (NGF) from mast cells,[12] thereby modulating nociception.

Ion channels and endogenous compounds

PEA is also able to activate various receptors and inhibit some of the ion channels involved in the rapid response to neuronal firing, including vanilloid receptor and K+ channels.[5] It also reduces the activity of COX, eNOS and iNOS thereby exerting anti-inflammatory and neuroprotective effects.[14] Oral supplementation with PEA has also been shown to increase plasma levels of other endogenous anti-inflammatory, neuroprotective and analgesic NAEs, including oleoylethanolamide (OEA) and the endocannabinoid anandamide (AEA).[15] It is thought that PEA increases endogenous levels of anandamide by inhibiting the expression of FAAH, the enzyme responsible for its degradation, allowing the anandamide to directly activate CB2 (or CB1) receptors and TRVP1 channels (entourage effect).[9]

PEA as a neuroprotective compound

PEA accumulates in brain tissue following injury, leading researchers to hypothesise that it may have neuroprotective properties and several preclinical studies support this proposition.[5] Daily dosing of PEA reduces experimentally produced memory deficit in a mouse model of Alzheimer's disease, via a PPAR-α – dependent mechanism.[16] Animal models also demonstrate that chronic administration of PEA is able to reduce some Parkinson's disease-related motor deficits,[17] and to ameliorate behavioural, biochemical and functional changes triggered by traumatic brain injury.[18]

Neuropathic and chronic pain

Neuropathic pain, caused by the damage or dysfunction of nerves, is often experienced as shooting, radiating, tingling, stabbing or burning pain. The compression of nerves, as found in sciatica or carpal tunnel syndrome, is a common cause of neuropathic pain. Other common causes include post-herpetic neuralgia (shingles), persistent post-surgical pain, diabetic neuropathy, pelvic pain, fibromyalgia and complex regional pain syndrome.[19,20]

Neuropathic pain is one of the most difficult chronic pain conditions to treat. The dynamic nature of the nervous system means that changes to its structure — for example damage caused by long-term compression or inflammation of the nerves – allow the nerves to continue to send pain signals to the brain long after the original cause of the pressure on the nerves has been removed. This "pain memory" can lead to "pain sensitisation" where the threshold of

pain receptors to stimuli is reduced, allowing even light touch of the affected area to induce the sensation of pain.[20]

The compression of nerves induces inflammation within the nerve and nerve root; this is largely mediated by inflammatory cells such as mast cells, which release pro-inflammatory prostaglandins and cytokines, which in turn trigger the synthesis of nitrogen monoxide[14] which causes vasodilation, promoting the infiltration of immune cells.[21] Metalloproteinases and other pro-inflammatory compounds are then produced, inducing the expansion and hyperactivation of connective tissue surrounding the nerves. This triggers the release of cytokines and other pro-inflammatory molecules[14] which act on receptors on the nociceptor nerve terminals, enhancing their responsiveness and leading to sensitisation. Microglia in the CNS may then be activated, propagating neuroinflammation through the recruitment of other microglia and astrocytes, thereby leading to chronic pain.[21]

PEA's ability to inhibit mast cell migration and activation, and the over-activation of glia and astrocytes, has led to it being extensively studied in neuropathic pain, where it is particularly effective in trapped nerve pain such as sciatica and carpal tunnel syndrome, as well as chronic pelvic pain, arthritis of the TMJ, and pain from molar surgery. A 2015 review of eight published clinical trials on the use of PEA in nerve entrapment syndromes in 1366 patients found PEA to be effective and safe in these conditions.[14]

Micronisation

The lipophilic nature of PEA requires specialised manufacturing and dosing considerations. PEA has a low solubility in water, and the absorption of orally administered PEA is limited by dissolution rate, with the amount absorbed related to particle size. Micronisation is frequently applied to highly lipophilic agents like PEA to reduce particle size and improve the bioavailability by increasing dissolution rate. The terms "micronisation" and "ultramicronisation" do not have strict definitions and therefore PEA products may be marketed using different definitions of these terms. According to the definitions used in the literature PEA may be classified as either: (i) unprocessed PEA (frequently referred to as naïve PEA or pure PEA; from 100 µm up to 2,000 µm); (ii) micronised PEA (PEA-m; 2–10 µm range); and (iii) ultramicronised PEA (PEA-um; 0.8–6 µm range).[22] **Clinical studies have demonstrated orally administered ultramicronised/ micronised PEA has a more favourable absorption profile and greater clinical effect than naïve PEA.**[22,23]

Clinical Research

Chronic pain of various aetiologies

A 2012 study on chronic pain[21] included 610 patients with ineffectively controlled chronic pain (NRS score ≥4) of various aetiologies: 331 with radiculopathy (including sciatica), 76 with failed back surgery syndrome, 54 with osteoarthritis, and the rest with herpes zoster infection (acute, persistent, and post-herpetic neuralgia), diabetic neuropathy, oncologic or other diseases. Apart from those with acute herpes zoster, all subjects had experienced pain for more than 6 months. 515 of the patients had poor pain control, but continued with their conventional analgesic therapies (antidepressants, anticonvulsants, opioids and NSAIDs) throughout the trial, while 95 had ceased use of conventional therapy due to side effects and so were using PEA alone; these two groups were distributed evenly according to aetiology and severity of pain. 564 subjects completed the study, and 46 dropped out; 16 due to good pain control, 20 for unspecified personal reasons, and 10 due to poor adherence to therapy.

Patients took 600mg of PEA twice daily for 3 weeks, and then 600mg once daily for the following 4 weeks, in addition to their previously established analgesic therapy, which was taken as fixed doses throughout the study period. The mean baseline NRS was 6.4 ± 1.4, and by the end of treatment the mean NRS had reduced to 2.5 ± 1.3 across all patient groups by aetiology or use of concomitant medication. This result was analysed to show that PEA treatment was the only variable to significantly affect the difference between baseline and end means ($p = 0.0001$). None of the concomitant therapies were found to impact the efficacy of PEA.

PAIN ASSESSMENT IN CLINICAL PRACTICE

The most common method of measuring pain clinically is the visual analog scale (VAS) to assess pain intensity. This is a simple 100mm line with no markings (numbers or descriptions) on which patients can mark their level of pain from 0 (no pain) to 10 (worst pain possible). The distance between the "no pain" end and the patient's mark is then measured in centimetres to give a score from 1–10. These are generally then interpreted according to the following: no pain (0–4mm), mild pain (5–44mm), moderate pain (45–74mm), and severe pain (75–100mm).[24]

The numeric rating scale (NRS) also rates pain from 0 (no pain) to 10 (worst possible pain) and results are highly comparable to VAS scores.[25]

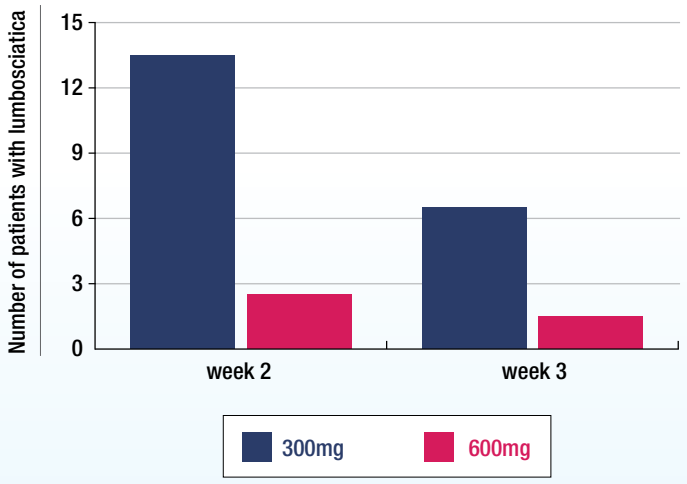
A score of three is often considered the maximum rating to qualify as tolerable pain.

Although all of the conditions have at least some degree of neuropathic pain, these results demonstrate that, unlike standard analgesics that only control single components of systemic pain, PEA can be applied to pain resulting from a diverse range of pathological conditions. This study also shows that PEA is safe and effective when taken concomitantly with standard analgesic medications.

Sciatica

A double-blind, placebo-controlled study published in 2010 assessed the efficacy of PEA in 636 patients with lumbosciatica over a period of three weeks. All patients had a VAS pain score of ≥5 at initial assessment, and were allowed to continue their usual treatments. On day 21, patients were assessed for pain using the VAS score, and quality of life using the 24 point Roland-Morris disability questionnaire (RDQ), and both patients and physicians gave a subjective analysis of treatment efficacy. Patients were assigned to either 300mg, 600mg or placebo. At the end of 3 weeks, patients taking 600mg had more than a 50% reduction in pain, from an average 7.1 to 2.1 on the VAS scale, while the reduction in pain in the placebo and 300mg groups was similar (6.6 to 4.6, and 6.5 to 3.6 respectively); the VAS difference between the groups had a p-value of <0.05. After 3 weeks of treatment, the NNT for the 600mg group was calculated as 1.5 (See Figure 5). At the 3 week point, RDQ scores had improved by an average of 3 points in the placebo group, 5 points in the 300mg group, and 9.2 points in the 600mg group to finish with an average score of 3.5 ($p<0.001$).[4] The 600mg dose was concluded to be significantly more effective than the 300mg dose ($p<0.05$).[26]

Figure 5: Number needed to treat (NNT) to reach a 50% reduction in pain on the visual analogue scale (VAS)



Diabetic Neuropathy

More than 50% of diabetic patients have some degree of peripheral neuropathy. This can significantly affect quality of life, with a particular impact on sleep and daily activities. A clinical trial in 30 patients with moderate symptoms of painful peripheral neuropathy resulting from compensated Type II diabetes mellitus (ie T2DM with blood glucose levels which are close to normal values) were given PEA at a dose of 300mg twice daily for 60 days. At the 60-day mark, significant improvements were measured in the patients' Michigan Neuropathy Screening Instrument, Total Symptoms Score, and Neuropathic Pain Symptoms Inventory scores ($p < 0.0001$). Furthermore, when assessed 30 days after ceasing use of PEA, there was no significant difference ($p>0.05$) between the 60 and 90 day results, demonstrating that the effects of PEA persisted after treatment was withdrawn.[27]

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-Induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy for which there is no established effective treatment. It has a complex, poorly understood pathophysiology, and causes pain, sensory changes and weakness, and occurs in as many as 68% of patients within the first month of chemotherapy treatment. In some cases, it is sufficiently severe to warrant a reduction in dose or cessation of chemotherapy treatment, and can significantly affect quality of life and a patient's ability to perform activities of daily living independently on an ongoing basis.[28]

A small clinical trial of PEA was run in 20 patients who had developed CIPN while undergoing treatment with bortezomib and thalidomide for multiple myeloma. After two months of treatment with PEA (300mg bd), patients had lower pain scores ($p<0.002$), and showed a partial improvement of all myelinated fibre groups as shown by neurophysiological measures. Both bortezomib and thalidomide are known to inhibit the activation of NF-κB, which in turn blocks transcription of NGF.[29] As NGF is known to modulate sensory and nociceptive nerve physiology,[30] the results of this study suggest that PEA has a normalising effect on NF-κB and NGF, rather than simply inhibitory.[12,29]

Knee Osteoarthritis

It has been shown that 26% of pain from knee osteoarthritis is neuropathic.[31] In a double-blind, placebo-controlled trial, 111 non-obese patients aged 38–76 years old with mild to moderate osteoarthritis were randomised to a daily dose of 300mg PEA, 600mg PEA, or placebo for 8 weeks in two separate doses with meals. Patients were only permitted paracetamol as a rescue medication, ceased use of all other osteoarthritis medications (pharmaceutical or complementary), and were excluded from the trial if they had used supplements including fish oil, glucosamine, chondroitin, or green-lipped mussel in the last 30 days. Pain, stiffness and function (assessed by WOMAC) improved in both PEA groups compared to placebo within 8 weeks (300mg PEA group $p = 0.037$, 600mg PEA group $p = 0.001$). Worst daily pain score measured by NRS reduced by 19.1% at week 1, 32.2% at week 4 and 40% by week 8 in the 300mg group. Pain score in the 600mg group was reduced by 21.5% at week 1, 32.2% at week 4 and

49.5% at week 8. Pain in the placebo group reduced by 12.7% at week 4 but returned to baseline at week 8. Pain reduction was significant in both the 300mg and 600mg groups ($p < 0.001$ for both).[32] (See Figure 6).

Figure 6: Pain reduction in osteoarthritis after PEA supplementation

Fibromyalgia

Fibromyalgia is a common condition affecting 2–5% of the population and is primarily seen in young and middle-aged women. It is characterised by widespread musculoskeletal pain and tenderness, poor quality sleep and significant fatigue, in addition to cognitive disturbances including poor concentration and memory, and high levels of distress. The underlying pathophysiology involves the development of "central sensitisation" changes in the CNS which result in usually non-painful stimuli being experienced as painful.[33]

A clinical trial in 35 patients who had undergone standard treatment with duloxetine and pregabalin for three months demonstrated that the addition of PEA to standard treatment for an additional three months (600mg bd for one month, then 300mg bd for two months) significantly improved VAS ratings from 3.7 to 1.9 ($p<0.0001$), and significantly reduced the number of Tender Points ($p<0.0001$).[34]

Depression

Emerging data demonstrates that the pathogenesis of major depression involves immuno-inflammatory markers including interleukin (IL)-1, IL-6 and TNF-α. Impairment of endocannabinoid signalling is also implicated in mood disturbances and other neuropsychiatric disorders. Due to PEA's anti-inflammatory and neuroprotective effects and its influence on cannabinoid receptor expression, it has been proposed as a beneficial adjunct to the treatment of depression.[35]

In a double blind, placebo controlled clinical trial, 58 patients with major depression (HAM-D score ≥19) were randomly assigned to either citalopram plus placebo, or citalopram plus PEA (600mg bd) for 6 weeks. At the two-week mark, the PEA group had a significantly greater reduction in HAM-D score than the placebo group, and at the end of the trial, response rate (measured as a ≥50% reduction in HAM-D score) in the PEA group was 100%, compared to 74% of patients taking citalopram alone ($p= 0.01$). Adverse events were similar between groups, with no serious adverse events and no related dropouts.[35]

Autism

PEA has been proposed as a potential adjunct to the treatment of autism, due to its anti-inflammatory effects and its role in protecting neurons against glutamate toxicity, two of the proposed key mechanisms in the aetiology of autism. In a placebo-controlled clinical trial, 62 children aged 4–12 years old were randomised to

receive either Risperidone and PEA (600mg bd) or Risperidone and placebo for 10 weeks. The PEA group showed a significantly greater reduction in hyperactivity than the placebo group ($p < 0.001$), and also in irritability ($p = 0.002$).[36]

Migraines

Migraine is thought to be a neurovascular pain syndrome with altered central neuronal processing (activation of brain stem nuclei, cortical hyperexcitability, and spreading cortical depression) and involvement of the trigeminovascular system.[37,38] Approximately one-third of individuals with migraine experience an aura phase, comprising neurological symptoms including visual, sensory, and language or brainstem disturbances.[37]

The pain, persistence and throbbing features of migraines are mediated by increased sensitivity (i.e. sensitisation) which results from neuropeptide release and mast cell activation which causes painful neuroinflammation in cranial vessels and the dura mater.[37,38] Thus PEA, which is known to regulate the activity of microglial cells and inhibit mast cell activation in both the central nervous system and periphery, may be able to reduce inflammation which contributes to the development of peripheral and central sensitisation that occurs in migraines. Furthermore, elevated PEA levels are found in the cerebral spinal fluid of patients with chronic migraine, and the analgesic endocannabinoid anandamide (AEA) levels are decreased, suggesting that increased PEA is required to counteract accelerated AEA catabolism.[39]

In an open study, 50 patients aged 18–65 years old suffering from episodic migraines without aura were treated with 600mg of PEA twice daily for three months.[40] Patients were allowed to continue with standard treatment including analgesics, anti-inflammatory or triptan therapies. All observed parameters significantly improved at the end of the study period including number of days per month with migraine, migraine intensity, monthly frequency of crises and analgesic use. The number of days per month with migraine decreased from a baseline average of 10.6 ± 0.7 to a value of 5.8 ± 0.7 at treatment end ($p<0.0001$). Migraine intensity diminished in 71.4% of patients and remained unchanged in only 28% of patients, whilst 16.3% of patients ceased all pharmaceutical migraine medication. Furthermore, thermographic imaging of the frontal area showed a reduction in hypothermia in >70% patients, which is believed to be due to vasodilation of the subcutaneous microcirculation that is under control of the autonomic system.[40] Thermographic improvement has been shown to closely parallel the clinical course of migraine.[41]

In a recent pilot study, twenty patients aged 33–56 years, suffering migraine with aura (≥2 attacks/month) received 1,200mg/d PEA in combination with NSAIDs (during acute attacks) for 90 days.[42] A further 20 patients were enrolled in a control group receiving a treatment of NSAIDs alone. PEA supplementation produced a reduction in pain scores which was evident at day 60 (T2) and lasted until the end of the trial (T3 = 90 days). At day 90 (T3) both the days of pain and the number of attacks/month were significantly reduced. In females the attacks per month decreased from 3.3 ± 0.8 to 1.5 ± 0.6 ($P = 0.000$) and the days of pain per attack decreased from 2.22 ± 0.6 to 1.1 ± 0.3 ($P = 0.000$). In males the attacks per month decreased from 2.93 ± 0.4 to 1.5 ± 0.5 ($P = 0.000$) and the days of pain per attack decreased from 2.85 ± 0.4 to 1.5 ± 0.6 ($P = 0.000$). A decrease in NSAIDs dosage was also observed. In the control group, the treatment with NSAIDs alone did not modify the pain intensity during the recurrence of attacks (T0: 3.15 ± 0.6; T3: T0: 3.1 ± 0.6, $P = 0.164$) or their number/month (T0: 2.85 ± 0.4; T3: 2.75 ± 0.4, $P = 0.08$).

Cold & Flu

Prior to the discovery of PEA's role in neuropathic pain, it was well known as a treatment for cold and flu. Six double blind, placebo controlled clinical trials in a total of almost 4000 subjects were published between 1969 and 1979. A daily dose of 1.8g (600mg tds) for 12 days was found to be an effective treatment for fever and pain (reduced by 45.5% compared to placebo). As a prophylactic, a loading dose of 1.8g per day (600mg tds) for 3 weeks then 600mg per day for 6 weeks, was found to significantly reduce the total number of sick days. PEA was shown to significantly reduce instances of serologically verified influenza infection ($p < 0.0002$).[6]

Further clinical research

Emerging evidence suggests that the anti-inflammatory effects of PEA may also be effective in conditions characterised by inflammatory intestinal hyper-permeability,[43] glaucoma,[44] and even in slowing down disease progression in Parkinson's disease.[45]

Dosage safety and clinical tips

Dosing – The daily dosage of PEA in clinical trials has ranged from 300mg–1200mg daily for chronic pain and up to 1800mg daily for acute colds and flu. Clinical trial data would suggest that a loading dose of 600–1200mg for 3–4 weeks followed by a maintenance dose of 300–600mg may be the most appropriate dosing strategy for chronic pain conditions. Individual requirements will vary.

Timing – Considering that PEA is a fat soluble compound, consumption with a fat-containing meal may enhance absorption.

Contraindications and adverse effects – There are no known contraindications. PEA has been clinically studied across a broad population group and has been found to be highly tolerable, with a side effect profile similar to placebo.

Table 1: Further clinical research

CONDITION	STUDY
Endometriosis	In an open-label pilot study, 30 women with laparoscopic diagnosis of endometriosis were treated with 600mg/d PEA BD for 10 days followed by PEA/polydatin (400mg + 40mg) BD for 80 days. At the end of the treatment, all patients showed a significant improvement in chronic pelvic pain, deep dyspareunia, dysmenorrhea, dyschezia, as well as in quality of life and psychological well-being.[46]
Endometriosis	Oral PEA (400mg) and polydatin (40mg) supplementation twice daily for 90 days improved pelvic pain in subjects with endometriosis and reduced analgesic use. Additionally, some improvements in endometriotic lesions were demonstrated by imaging.[47]
Endometriosis	Subjects with endometriosis receiving oral PEA (400mg) and polydatin (40mg) supplementation twice daily for 90 days reported significant decreases in chronic pelvic pain, dyspareunia and dysmenorrhea within 30 days of treatment.[48]
Endometriosis-associated chronic pelvic pain	Oral PEA (300mg) and α-lipoic acid (300mg) supplementation twice daily for 9 months significantly improved pain symptoms and all categories of quality of life by 6th and 9th months in women with endometriosis-associated pelvic pain.[49]
Glaucoma	300mg PEA BD for 6 months reduced intraocular pressure and improved visual field indices in subjects with normal tension glaucoma.[50]
Parkinson's disease	Addition of 600mg/d PEA to levodopa for 1 year significantly reduced most non-motor and motor symptoms, indicating that the addition of PEA may slow disease progression and disability in Parkinson's disease patients.[45]
Inflammation induced intestinal permeability	Participants were randomised to receive either 600mg aspirin + placebo or 600mg aspirin + 600mg PEA. In participants receiving placebo only, aspirin administration caused an increase in the urinary concentration of mannitol and lactulose over the 6-hour study period. Absorption was decreased in the PEA group, suggesting PEA may reduce inflammatory intestinal hyperpermeability.[43]
Burning mouth syndrome	600mg PEA BD for 60 days significantly reduced burning mouth sensation compared to placebo in patients with burning mouth syndrome.[51]
Irritable Bowel Syndrome	In a 12 week DBPCRCT, PEA/polydatin (200 mg/20 mg) BD significantly improved abdominal pain severity in IBS patients compared to placebo, but did not significantly reduce mucosal mast cell counts.[52]
Relapsing-remitting multiple sclerosis	In a 12 month DBPCRCT, 600mg/d added to IFN-β1a injections (3 times per week) improved in pain sensation without a reduction of the erythema at the injection site in patients with relapsing multiple sclerosis. A significant improvement in QoL was observed. PEA also had beneficial effects in terms of reducing circulating proinflammatory cytokines, pain sensation, and increasing NAE levels.[15]
Vulvodynia	Case report: After 3 months of topical baclofen 5% and oral PEA 400 mg, TID, symptoms decreased by more than 50% in a female chronic vulvodynia and proctodynia, and she was able to have sexual intercourse again without pain.[53]

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