White Paper: PEA

BACKGROUND AND HISTORY

The compound known as PEA was first formally recognised in 1957 when it was isolated as a food component in a number of plant and animal sources. Palmitoylethanolamide (PEA) is a fatty acid amide that is known to exert a range of effects on both the peripheral and central nervous systems (CNS).[1] PEA is classed as an ALIAmide (autocoid local injury antagonist amide), a family of molecules involved in biological processes, including lipid metabolism, nociceptor inhibition and downregulation of inflammation.[2] This lipid mediator is endogenously produced and metabolised in all animal and human cells through the cell membrane's lipid bilayer. Although PEA is expressed in all body tissues, it is found most abundantly in the central nervous system and, being produced in certain areas of the brain, it is also considered to have neuromodulatory effects.[21] The enzyme used in the production of PEA and all *N*-acyl-ethanolamines (NAEs) is the phospholipase enzyme *N*-acyl-phosphatidyl-ethanolamine D (NAPE-PLD). NAPE-PLD hydrolyses the PEA precursor *N*-palmitoyl-phosphatidyl-ethanolamine.[3] As a cannabimimetic compound and lipid messenger,[6] PEA is also a member of the endocannabinoid system, exerting an effect on cannabinoid receptors.

PEA is most commonly found in the following food sources[1]:

- Egg yolks
- Dairy milk
- Soy products (including beans, oil, and lecithin)
- Peanuts (and peanut oil)
- Human breast milk
- Peas
- Tomatoes
- Corn

MECHANISMS OF ACTION

Mast cells

The anti-inflammatory action of PEA has been established since at least 1965, based on the findings of Kuehl, et al from 1957 who reported finding that a fraction found in egg yolks had an anti-inflammatory and immune enhancing effect.[22] In 1996, a research group proposed the mechanism of action of PEA; operating as an ALIAmide, the compound downregulates mast cell activation. The inhibition of mast cell degranulation results in a decreased release of other bioactive pro-inflammatory mediators, including tumour necrosis factor-α (TNF-α), histamine, interleukins and prostaglandins.[23]

PPAR-a

Future studies revealed that PEA also functions by directly activating the receptors peroxisome proliferator activated receptor-α (PPAR-α) and orphan G-coupled protein receptor 55 (GPR55). As a PPAR-α agonist, PEA plays a role in inflammatory gene suppression, inhibiting chemokine expression and thereby reducing neuropathic pain.[29] This is just one way in which PEA is known to operate as an antinociceptive or analgaesic agent.

Glial cells

Glial cells are central cells in the pathogenesis of neuropathic pain and hypersensitivity.[49] PEA is shown to protect glial cells, particularly microglia, from excitotoxicity, therefore PEA is able to control the activity of microglial cells, even reversing hyperactive cells in the spinal cord. This suggests a significant role for PEA in neuropathic pain.[23]

Cannabinoid receptors

PEA belongs to the endocannabinoid family, a group of bioactive endogenous lipid mediators that bind to cannabinoid receptors. Cannabinoid receptor 1 (CB1) is found predominantly in the CNS and the central and peripheral levels of the pain pathways,[24] while cannabinoid receptor 2 (CB2) is found in cells involved in immune function. It's also thought that certain cannabinoids may modulate PPARs. PEA may also indirectly activate CB1, CB2, as well as transient receptor potential vanilloid type 1 (TRPV1) receptors.[1] The indirect action on the CB1 and CB2 receptors is thought to take place via the 'entourage effect', whereby anandamide activity is enhanced, or through an as yet unidentified 'CB2-like' receptor.[30] The analgaesic effect exerted by cannabinoids is predominantly actioned through the CB1 receptor by inhibiting pre-synaptic gamma-aminobutyric acid (GABA), as well as glutamatergic transmission.[25]

Cyclo-oxygenase-2 (COX2)

The enzyme COX-2 is responsible for the synthesis of pro-inflammatory prostaglandins. PEA suppresses inflammation via its action as a COX-2 inhibitor, resulting in anti-inflammatory and analgaesic effect.[7,28]

BIOAVAILABILITY OF LEVAGEN+™

Levagen+™ uses a novel dispersion technology system by LipiSperse® to create a pharmacokinetic PEA formulation. The low water solubility and therefore poor absorption of micronised PEA formulations has meant that most standard formulations are less likely to yield positive therapeutic outcomes. The surfactants, polar lipids and solvents in LipiSperse® combined with PEA crystals increases the distribution of lipophilic PEA

in aqueous environments. The result is a measurable increase in absorption of Levagen+™ when compared to standard formulations on the market. Increased plasma concentrations of PEA were seen in the group receiving Levagen+™ above baseline concentrations by 1.75 times, compared to the group receiving the standard formulation of PEA.[5]

The benefits of Levagen+™ and the LipiSperse® technology include:

- Increased functionality
- highly dispersible in cold water
- higher active PEA load
- increased bioavailability
- effective particle distribution.

CLINICAL USES OF PEA

Pain – Neuropathic pain, chronic pain, sciatica, migraines

Due to the many mechanisms by which PEA exerts anti-inflammatory, analgaesic and antinociceptive actions, it has been utilised in a broad range of studies into numerous pain conditions with varying pathologies, including acute, neuropathic, chronic, inflammatory, unmanageable, and postoperative pain.[7] A number of clinical trials support the safe and efficacious use of PEA as an analgaesic for nerve compression syndromes such as sciatica and carpal tunnel syndrome.[8] Migraines are a notoriously difficult to treat pain condition where PEA can be safely used as a prophylactic treatment in both adults and children, with one study showing a reduction in both pain intensity and number of attacks per month in paediatric migraine sufferers.[9] Migraine with aura has also been treated post-migraine onset with ultra micronised PEA as pain relief with a statistically significant benefit.[10]

Osteoarthritis

As a condition with pain and disability at the centre of its symptomatology, osteoarthritis (OA) is often poorly managed and can lead to a reduced quality of life. Due to the presence of low-grade inflammation and oxidative stress in patients with osteoarthritis, PEA has been considered an effective tool in ongoing pain management for OA. One placebo-controlled, double-blind, randomised clinical trial using 600mg/day of PEA for eight weeks as a stand alone treatment found it to be safe and effective in the management of OA. Evidence currently suggests that the actions of PEA in alleviating the inflammation and pain of OA include working at both the central and peripheral nervous systems to reduce nociceptive and neuropathic elements. PEA is considered safe and effective in the management of OA and its associated symptoms.[13]

Fibromyalgia

Fibromyalgia syndrome patients are benefiting from the use of PEA as an effective treatment for a number of symptoms. It has been shown to be of particular benefit for those requiring long-term treatment as it is well-tolerated.[14] The use of PEA alongside common medications for the treatment of fibromyalgia is also generally considered safe; one study that considered the efficacy of treatment of duloxetine and pregabalin in combination with PEA found that there was an added analgaesic benefit, with subjects receiving the combination treatment having significantly reduced pain symptoms.[15]

Depression

PEA is shown to have anti-depressant effects either as a standalone treatment or in combination with other types of anti-depressant medications. Preclinical studies assessing the impact of PEA in depression associated with traumatic brain injury (TBI), as well as neuropathic pain, have so far yielded promising antidepressant activity. The antidepressant mechanisms of action of PEA include the targeting of PPAR-a and the endocannabinoid system where PEA binds to the GCPR55, as well as a weak affinity for the CB1 and CB2 receptors.[16] A 2018 study into the efficacy of PEA in major depressive disorder (MDD) found that 600mg administered twice daily as an adjunct treatment with citalopram concluded that PEA resulted in a rapid onset of antidepressant effects and a n improvement in the Hamilton Depression Rating Scale. This study also states that PEA targets the N-methyl-D-aspartate (NMDA) receptor, a ligand of glutamate—NMDA receptors are a less discussed target for antidepressant activity.[17]

Autism

The combination of inflammation and glutamate excitotoxicity are thought to be part of the pathogenesis of autism. As an endocannabinoid, PEA is shown to simultaneously inhibit glutamatergic toxicity and down-regulate inflammation. A recent 2018 randomised, placebo-controlled, double-blind, parallel group trial looking at co-treatment with risperidone (an atypical antipsychotic) and PEA over 10 weeks in children with autism found that the treatment group had significant amelioration of hyperactivity symptoms, irritability and non compliance when compared to the placebo group.[18] A further 2016 case study with an autistic patient treated with a combination of ultra micronised PEA and luteolin resulted in a reduction in most of the indices of hyperactivity, motor stereotypies, as well as improved sociability. The treatment was also well tolerated by the 10 year old patient in this case study.[19]

Cold & Flu

Inflammation is the first response in the immune defense against both physical and biological agents such as viruses and bacteria.[3] With a well-established action as an anti-inflammatory, PEA therefore also influences the immune response. Numerous trials have been conducted over decades to assess the efficacy of PEA in reducing cold and flu symptoms. All trials resulted in some common clear treatment outcomes: PEA can be used as an influenza prophylactic without side effect to significantly

reduce incidence of flu; acute respiratory diseases were significantly reduced after administration with PEA; symptoms of influenza were significantly less in PEA treated groups.[4]

Gastrointestinal disorders

Inflammation-based gastrointestinal (GI) disorders are being treated with PEA due to the multitude of anti-inflammatory actions of the therapeutic agent. Crohn's disease and ulcerative colitis (UC) are two of the most commonly diagnosed irritable bowel diseases (IBD) with chronic inflammation at the core of pathogenesis. Recent research has shown that angiogenesis is a significant process in the chronic inflammation pathology. Angiogenesis is also involved in immune dysregulation and carcinogenesis. The action of PEA has been shown to inhibit inflammation-based angiogenesis in the colonic mucosa associated with UC, reducing new vessel formation and mucosal damage.[11] Preliminary evidence also suggests that PEA suppresses cytokine synthesis in human colonic explants from IBD and bowel cancer resections.[20]

Endometriosis

The involvement of mast cell degranulation in endometriosis forms part of the inflammatory basis of the disease. PEA has been shown in numerous studies to suppress mast cell degranulation, thus reducing the release of histamine, along with the activation of other pro-inflammatory mediators, including TNF-α and prostaglandins.[26,23] Mast cell involvement in endometriosis is believed to contribute to the pain experienced in endometriosis, possibly through nerve involvement.[26]

A number of clinical trials have investigated the combined effects of PEA and polydatin (a derivative of resveratrol) in reducing pelvic pain associated with endometriosis. An open-label pilot study on endometriosis sufferers and the use of ultra micronised PEA in combination with polydatin was found a significant reduction in pain symptomatology, an improvement in quality of life and psychology wellbeing, and showed no serious side effects.[27]

Safety data, cautions and contraindications

No clinically relevant drug-drug interactions or dose-limiting side effects have been reported in the use of PEA.[22] As both an analgaesic and anti-inflammatory agent, PEA has demonstrated both high safety and high tolerability.[1,31]

CLINICAL RESEARCH

Subject	Trial outcome
Exercise recovery in males	Double-blind, randomised, placebo-controlled study, 28 young male participants were given either liquid PEA at **167.5mg/d** Levagen+ or placebo and were then asked to perform leg press exercises consisting of four sets at 80% of one repetition. The study found that PEA reduced blood lactate and myoglobin concentrations and increased protein kinase B phosphorylation post-exercise, aiding in muscle recovery.[6]
Increased absorption of PEA using novel dispersion technology system (Lipisperse)	Double-blind, parallel study assessing absorption rates of Levagen+ PEA formula, 28 healthy male and female participants were given either a **300mg** dose of PEA with LipiSperse® or 300mg unprocessed PEA. The findings revealed PEA as Levagen+ increased plasma PEA concentrations by 1.75 times that of the standard formulations within 45 minutes of ingestion.[5]
PEA in prevention and treatment of influenza and common cold	Review article assessing the results of 6 clinical trials into the use of PEA as a treatment for colds and flu. The authors concluded that based on the results of the 6 trials, PEA should be considered as a treatment for flu and respiratory infections due to both its efficacy and lack of side effects.[4]
Efficacy of PEA in combination with antioxidant molecules	Trials combining PEA with antioxidant molecules luteolin, quercetin, polydatin, silymarin, and baicalein were reviewed for the efficacy in counteracting inflammation. The authors concluded that PEA was able to act effectively in synergy with the antioxidant molecules to reduce inflammation and can be a valid alternative to anti-inflammatory drugs.[3]
Knee osteoarthritis	Randomised, double-blind, placebo-controlled study assessing safety, tolerability and efficacy of PEA in reducing symptoms of knee OA used randomised doses of **300mg and 600mg in divided doses BID** for 8 weeks. The results showed a significant reduction in total WOMAC score, WOMAC pain and stiffness scores in both the 300mg and 600mg groups. The 600mg group also experienced a significant improvement in WOMAC function score compared to placebo. Both treatment groups also experienced reductions in anxiety as measured by a DASS score, compared to placebo. The PEA was well tolerated.[13]
Temporomandibular joint inflammatory (TMJ) pain	Triple-blind, randomised clinical trial assessing efficacy of PEA versus ibuprofen NSAID for pain relief in TMJ pain. 120 patients were divided into two groups; group A received PEA at **300mg a.m. and 600mg PEA p.m. for 7 days, then 300mg BID for 7 more days, group B received 600mg ibuprofen 3 times a day for 2 weeks**. Decrease in pain was significantly higher in group A after 2 weeks treatment.[32]
Low back pain	Pilot study assessing efficacy of um-PEA as add-on therapy to Tapentadol (TP) in patients with low back pain. Patients retrospectively treated with TP for 6 months were then treated with um-PEA combined with TP for another 6 months. The results showed a stastically significantly higher reduction in pain intensity and degree of disability in PEA and TP treatment, compared to TP treatment only.[33]
Sciatic pain and carpal tunnel syndrome	Review of 8 clinical trials assessing efficacy of PEA in alleviating different nerve compression syndromes, including sciatica and carpal tunnel syndrome pain. PEA at between **300mg BID and 600mg** once and up to twice daily was found to be effective in relieving pain associated with a variety of nerve compression syndromes with or without concomitant established analgaesic use.[8]
Fibromyalgia	A retrospective observational study analyzing data on 407 patients with fibromyalgia prescribed um-PEA, with or without concomitant pharmaceutical treatment. PEA was found to be well-tolerated and suitable for patients requiring long-term treatment. The study also revealed statistically significant changes in pain and quality of life scores.[14]

CLINICAL RESEARCH (CONTINUED)

Subject	Trial outcome
Fibromyalgia	Assessment of the results of both a prospective and a retrospective observational study using a combination of duloxetine (DLX), pregabalin (PGB) and PEA to exert anti-inflammatory and analgaesic effects in fibromyalgia. In both studies, significant decreases were seen in tender points and pain intensity after 3 months of treatment. The prospective observational study utilised **600mg BID in month 1 and 300mg BID in months 2-3**.[15]
Carpal tunnel syndrome (CTS)	A randomised controlled trial utilising **600mg/d or 1,200mg/d** of PEA over 30 days in patients with moderate CTS was compared to a control group receiving no treatment. PEA was found to significantly improve CTS induced nerve latency time, with Tinel's sign presence and discomfort also reduced. The study found the significance of the results were dose-dependent.[34]
Carpal tunnel syndrome	42 patients awaiting surgery for CTS experiencing sleep disorders and painful symptoms were included in an open, controlled, randomised study. Group 1 received um-PEA at **600mg BID** pre and post-surgery, group 2 did not receive treatment. Significant improvement was found in group 1 pre-surgery in overall sleep quality and latency, as well as mitigation of painful symptoms.[35]
Diabetes associated neuropathic pain	Study evaluating effectiveness of micronised PEA in reducing pain in diabetic patients with peripheral neuropathy. 30 diabetic patients with diabetic neuropathy were administered PEA at **300mg BID** for 60 days. Analysis indicated significant reduction in pain severity and related symptoms. No serious side effects were reported and the treatment was well tolerated.[36]
Peripheral neuropathic pain (NP)	A prospective, short-term study assessing um-PEA treatment for peripheral neuropathic pain. 30 patients with diabetic or traumatic chronic neuropathic pain not currently managed by other conventional therapies were administered PEA at **1,200mg/d**. PEA demonstrated a high level of efficacy in reducing hyperalgesia, and improving scores related to paresthesia and dysesthesia.[37]
Major depressive disorder (MDD)	A randomised, double-blind, placebo-controlled study involving 58 patients diagnosed with MDD were randomised to receive either **600mg BID** or placebo, in conjunction with citalopram, for 6 weeks. The results showed that PEA in combination with citalopram is an effective treatment in improving symptoms of MDD.[15]
Autism	**600mg BID** of PEA was co-administered with risperidone over a 10 week period in a randomised, parallel group, double-blind, placebo-controlled trial involving 70 children (aged 4-12 years) with diagnosed autism and moderate to severe irritability. At week 10, the combination treatment was shown to have greater efficacy in ameliorating irritability and hyperactivity compared to the risperidone and placebo treated group.[18]
Autism	An assessment of two cases wherein PEA was administered to two children with autism. The first, a 13 year old male, experienced significant improvement in atopic symptoms, language, overall autism severity measures after treatment with administration of PEA at **600mg BID**. The second case, a male aged 15 years, experienced rapid improvements in cognition, behavior and sociability after administration of PEA at **600mg/d**.[38]
Chronic Pain	Observational study involving 610 patients unable to control chronic pain using standard therapies. PEA at **600mg BID** was administered for 3 weeks, **600mg/d** was given for the final 4 weeks either alone, or in addition to, standard therapy. PEA markedly decreased mean score pain intensity in all patients independent of associated pathological condition.[39]

CLINICAL RESEARCH (CONTINUED)

Subject	Trial outcome
Migraine	Open pilot study to verify efficacy of um-PEA in reducing frequency and severity in migraine sufferers when used as a prevention. 50 patients suffering migraine without aura were administered PEA at **600mg BID** for 3 months. Symptoms were considerably improved in most patients, while some remained unchanged. Significant reductions were seen in migraine frequency, with some patients reporting a reduction in use of analgesics.[40]
Ocular hypotension (OH)	A prospective, randomised, double-blind crossover clinical trial involving 42 patients with primary open angle glaucoma (POAG) and OH were treated with PEA at **300mg BID** or placebo over a 2 month period. Intraocular pressure was measurably reduced in the group receiving PEA compared to placebo.[41]
Ocular Hypertension	A randomised, double-blind, placebo-controlled crossover single-centre study involving 40 OH patients without prior treatment assessed the impact of PEA on endothelial function and IOP. PEA was administered to group A at **300mg BID** over 3 months, group B received a matching placebo. PEA reduced IOP and improved endothelium-dependent flow-mediated vasodilation.[42]
Myasthenia Gravis	A pilot study to analyse the beneficial effects of PEA in patients with myasthenia gravis and symptoms of muscular fatigue and neurophysiological changes. The study which utilised **600mg BID** for one week significantly reduced the level of disability and decremental muscle response.[43]
Neuropathic pain	This case series assessed 7 patients experiencing neuropathic pain with varying pathogeneses. Each case was given between **300mg-600mg BID**. Assessment of all cases revealed PEA as a promising therapeutic treatment for neuropathic pain with high tolerability and low potential for side effects.[44]
Chemotherapy-induced neuropathy	A study assessing efficacy of PEA in 20 patients experiencing chemotherapy-induced painful neuropathy. Patients were administered PEA at **300mg BID**. Significant improvements were found in all pain and neurophysiological measures, with PEA restoring significant nerve function.[45]
Idiopathic trigeminal neuralgia	A case series involving 10 patients with idiopathic trigeminal neuralgia treated with PEA in combination with established medications. PEA was administered at **1,200mg for 10 days, then 600mg** for a further 20 days. Slight improvements in pain intensity were reported by 3 of the patients.[46]
Endometriosis	A preliminary observational study into treatment of endometriosis associated pelvic pain with PEA in 4 patients over 3 months. **400mg PEA with 40mg polydatin was administered BID for 90 days**. Pain relief was observed after 1 month of treatment, with reduction in analgaesic medication observed in all patients.[47]
Endometriosis	A prospective study was conducted to evaluate the effects of combined PEA with transpolydatin as pain relief for endometriosis pain. 47 patients were split into two groups depending on site of endometriosis (recto-vaginal septum or ovarian). Each group received **400mg/d PEA and 40mg/d transpolydatin** over a 90 day period along with concomitant therapy of either oestrogen-progestin pill or anti-inflammatory drugs. Intensity of pain decreased significantly for both groups. Dysmenorrhoea reduced more rapidly in the group with predominantly ovarian endometriosis.[48]
Depression	A literature review on current use of PEA as an antidepressant was conducted, with findings revealing that PEA has potential antidepressant effects as a standalone treatment, or in combination with other types of antidepressant medications.[28]