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The Potential Benefits of Palmitoylethanolamide in Palliation: A Qualitative Systematic Review

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Abstract

Palmitoylethanolamide (PEA) is a nutraceutical endocannabinoid that was retrospectively discovered in egg yolks. Feeding poor children with known streptococcal infections prevented rheumatic fever. Subsequently, it was found to alter the course of influenza. Unfortunately, there is little known about its pharmacokinetics. Palmitoylethanolamide targets nonclassical cannabinoid receptors rather than CB1 and CB2 receptors. Palmitoylethanolamide will only indirectly activate classical cannabinoid receptors by an entourage effect. There are a significant number of prospective and randomized trials demonstrating the pain-relieving effects of PEA. There is lesser evidence of benefit in patients with nonpain symptoms related to depression, Parkinson disease, strokes, and autism. There are no reported drug–drug interactions and very few reported adverse effects from PEA. Further research is needed to define the palliative benefits to PEA.

Keywords

palmitoylethanolamide, pain, neuropathy, depression, autism, Parkinson disease, stroke

Introduction

N-palmitoylethanolamide (PEA) is an endogenous cannabimimetic saturated fatty acid available as a nutraceutical which targets multiple potential noncannabinoid receptors and ion channels.[1-4] Related endogenous cannabinoids are N-arachidonoyl ethanolamine (AEA), also known as anandamide, 2-arachidonoyl glycerol (2-AG), and oleoyl ethanolamine (OEA). Palmitoylethanolamide does not bind to classical cannabinoid receptors (CB1, CB2) to any significant degree and only indirectly activates classical receptors through an entourage effect. The main targets of PEA have been clinically associated with analgesia, antidepressant, and antineuroinflammatory activity and are peroxisome proliferator-activated receptor α (PPAR), the vanilloid receptor TPRV1, the orphan receptor GPR-55, and indirectly through alterations in monoamine neurotransmission and classical cannabinoid receptors. There are both animal and clinical studies that have demonstrated analgesia with PEA as a single agent and in conjunction with other analgesic.[2-12] In addition, PEA may be clinically helpful in a wide range of neurological disorders such as depression, Parkinson disease (PD), autism, and strokes.[13-16] The purpose of this review is to make clinicians aware of the benefits to PEA when treating various symptoms and disease.

Method

We did a PubMed search using the term "palmitoylethanolamide" which generated 707 references. We then did individual searches using the terms, "palmitoylethanolamide and pain," which generated 209 references, "palmitoylethanolamide and appetite," 18 references, "palmitoylethanolamide and Alzheimer's disease," 14 references, "palmitoylethanolamide and heart," 25 references, "palmitoylethanolamide and COPD 0 references," "palmitoylethanolamide and stroke, 12 references," and "palmitoylethanolamide and age," 20 references. Hand searches were made of multiple reviews and clinical studies for completeness. A meta-analysis has been reported recently on the use of PEA for pain and no additional studies were available.[11] Forty-seven clinical studies were then summarized in 5 tables. The first 4 tables are a summary of studies using PEA for pain and the last table summarizes the studies of PEA for nonpain symptoms in various diseases.

History of PEA

Palmitoylethanolamide was discovered more than 60 years ago as a biologically active nutrient in soybean lecithin, egg yolks, and peanut meal. It was the active component that blocked passive joint anaphylaxis in guinea pigs.[17] Even earlier and

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clinically relevant, Coburn described the clinical benefits to feeding poor children dried egg yolks to prevent rheumatic fever despite streptococcal exposure. This observation leads to the discovery of PEA a decade and a half later.[18,19] Palmitoylethanolamide was eventually isolated in 1957 and was found to be a fatty acid component in guinea pig and rat brain.[20,21] In the 1960s, SPOFA United Pharmaceuticals brought PEA to market as 300 mg Impulsin. The nutraceutical was promoted as a treatment for influenza and the common cold. Multiple studies at the time demonstrated that PEA reduced viral symptoms and clinical influenza.[22,23] It was later found that PEA reduced the viral serology of the influenza virus.[24] This benefit has largely been ignored in the recent literature, which now is largely concentrated on PEA benefits as an analgesic and modulator of neurological disorders.

Pharmacokinetics

N-acyl ethanolamines (NAEs) are derived from plasma membranes by a 2-step process. N-acyl ethanolamines differ from anandamide and 2-AG in that they do not bind to classical cannabinoid receptors. The most common NAEs are OEA and PEA, with PEA being the most abundant. The first involves the transfer of palmitic acid to a phospholipid donor by a calcium-dependent N-acyl transferase (NAPE). The second step involves removing the phosphatidyl group by NAPE phosphatase.[25,26] Palmitoylethanolamide is produced on demand. Local tissue levels are highly regulated through a balance between synthesis and catabolism. Palmitoylethanolamide is metabolized intracellularly by fatty acid amide hydrolase (FAAH). Within the cell, PEA binds to fatty acid binding protein and heat shock protein.[27] Palmitoylethanolamide can also be metabolized by N-acyl acid amidase to palmitic acid and ethanolamine. It competes for FAAH with AEA and by this entourage effect increases levels of AEA, thus indirectly activating classical cannabinoid receptors.[28-30]

Little is known about the pharmacokinetics of PEA in humans. The bioavailability and apparent volume of distribution have not been studied. Diet changes in palmitoyl do not influence circulating levels and diet changes in omega fatty acids do not change NAE blood levels.[31,32] Fasting blood levels of PEA range from 3 to 24 ng/mL and, at least in animals, do not accurately reflect levels in the peripheral compartment (central nervous system [CNS]).[33] In animals, NAE brain levels diminish with age. The commercial form of PEA (either micronized or ultramicronized) has increased bioavailability in animals compared to nonmicronized forms, but there are no clinical data to suggest this is true for humans.[34,35] There is little known about how PEA penetrates tissues or whether diseases or inflammation influence distribution, clearance, or PEA circulating half-life.[31] However, if animal models reflect what occurs clinically, PEA levels are increased either systemically or regionally in the face of neuropathic injury and inflammation. This may be due to downregulation of FAAH.[36] In rodents, PEA is the most abundant NAE in tissues, with levels ranging from 78 to 50 000 pmol/g in tissue.[37-39] Paradoxically, PEA concentrations in leukocytes are reduced in chronic inflammation, which may reflect reduced production or increased release and PEA depletion over time with chronicity of the disease process.[40,41]

The distribution of PEA within the brain is highly variable despite being a saturated acyl ethanolamine.[42] The distribution does not follow the primary PEA target, the PPAR-α receptor.[37] In animals, there is a diurnal variation in CNS PEA. Palmitoylethanolamide generally increases in light and increases selectively in the pons, hypothalamus, and hippocampus when lights are off, presumably increasing sleep behaviors and reducing feeding behaviors.[37] In vitro, PEA has been shown to be produced not only by neurons but also by astrocytes and in greater quantities than AEA (production ratio of 26:1).[43]

Pharmacodynamics

Palmitoylethanolamide levels in the peripheral compartment (CNS) may be an important clinical site of action. There is an inverse relationship between PEA levels in the CNS and pain in animal models.[44,45] N-acyl ethanolamines interact with multiple receptors and ion channels with a multitude of biological effects. As mentioned, PEA does not directly interact with CB1 or CB2 receptors. In animal models, PEA reduces appetite (though not demonstrated clinically), reduces the rewarding effects of nicotine and cocaine, improves neuropathic and inflammatory pain, improves cardiac failure, reduces Alzheimer type dementia, acts as an antidepressant, and reduces brain damage from strokes and brain trauma.[2-4,46-50]

Palmitoylethanolamide is an agonist for the PPAR-α receptor, which is a critically important receptor in downmodulating neuroinflammation.[9,51] The PPAR-α receptor also mediates mood, pain, and neuroinflammation, as demonstrated in animals. Palmitoylethanolamide bound to PPAR-α receptors forms heterodimers with retinoic acid receptors. The dimer acts as a transcription factor promoter of peroxisome proliferator response elements.[52] Palmitoylethanolamide also increases the expression of PPAR-α messenger RNA.[53] Interactions with response elements results in downregulation of nuclear factor κB (NF-κB) and subsequent downstream signaling cascades which are the "gateway" to neuroinflammation. The NF-κB inhibitor, inhibitory I-κ (Iκ-B), is upregulated. The NF-κB is responsible for upregulating inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 1 and 6 as well as cyclooxygenase 2.[30,50,54-60] Activation of PPAR-α increases the production of intracellular neurosteroids, which alters calcium channels and big conductance potassium channels leading to hyperpolarized neurons.[9,61] This accounts for the antiseizure activity of PEA in animal models.[62] Allopregnanolone, one of the principal neurosteroids, reduces pain, prevents seizures, and reinforces γ amino butyric acid (GABA) signaling.[61,63,64] Palmitoylethanolamide and downstream allopregnanolone reduce stress in animals and post-traumatic stress disorder (PTSD)-like behaviors in animal models. Stress and PTSD reduce pain thresholds.[65] The antiallodynia effects of

PEA are dependent on the presence of PPAR-α receptors. This has been demonstrated in animal models of paclitaxel-induced and diabetic neuropathic pain.[66,67] Palmitoylethanolamide increases CB2 receptor expression through PPAR-α activation.[68] This upregulation of CB2 on microglia facilitates AEA and 2-AG downmodulation of neuroinflammation as an entourage effect of PEA.

There are several other benefits to PPAR-α receptor activation. Activation of PPAR-α receptors and subsequent neurosteroid production has an antioxidant effect, which increases resistance to reactive oxygen species.[69] The PPAR-α agonists cause a release of oxytocin from the supraoptic and paraventricular hypothalamic nuclei which project to the amygdala, raphe nuclei, and dorsal horn. This pathway is associated with antinociception in animal models.[70,71]

Palmitoylethanolamide interacts with vanilloid receptors in a unique manner. Palmitoylethanolamide is a positive allosteric modulator of the transient receptor potential vanilloid-1 (TRPV1).[1,10] This is the same receptor that is activated by capsaicin and AEA. Paradoxically, PEA accelerates TRPV1 receptor desensitization.[72] The interactions with the TRPV1 receptor contribute to analgesia and anti-inflammatory activity and vasorelaxation.[1,10,73,74] Perivascular sensory nerves express TRPV1. Palmitoylethanolamide is present in significant concentrations in perivascular sensory neuron areas. The binding of TRPV1 by AEA and PEA causes vasorelaxation.[75]

Palmitoylethanolamide activates the orphan receptor GPR55.[76,77] Although PEA increases GABA neurotransmission, through GPR55, PEA also reduces GABAergic tone by increasing postsynaptic 2-AG production that binds to presynaptic CB1 receptors, which in turn reduces GABAergic tone.[78] Activation of GPR55 increases dopaminergic neurotransmission in the hippocampus.[79] One would assume that this increase in dopamine in the mesolimbic system would increase the rewarding or "drug-liking" effects of addicting drugs, but in fact this leads to a reduction in the morphine rewarding effects in animals.[80-82] Paradoxically, PEA blocks the increased dopamine neurotransmission associated with nicotine, reducing its rewarding effect also.[47] This action may also be through PPAR-α.[83] Palmitoylethanolamide blocks cocaine behaviors in animals as measured by conditioned place preference.[84] GPR55 is highly expressed in the gastrointestinal tract and modulates inflammatory responses.[85] Palmitoylethanolamide has the potential to influence intestinal motility, secretion, inflammation, and cellular proliferation, not only through GPR55 but also by way of PPAR-α and the entourage effect on CB1 and CB2.[86,87]

Mast cells within the CNS sustain neuroinflammation and disrupt the blood–brain barrier.[46] Mast cells migrate into the CNS through penetrating blood vessels and release biogenic amines, thus contributing to demyelination and neuropathic pain associated with neuroinflammation.[88,89] Mast cells play a role in brain ischemia, spinal cord compression, and amyotrophic lateral sclerosis.[90,91] Mast cells interact with glia through Toll-like receptors, complement receptors, and CD40 receptors to amplify neuroinflammation.[92,93] Palmitoylethanolamide and the antioxidant luteolin reduce mast cell–mediated toxicity caused by brain ischemia in animals.[94] Palmitoylethanolamide has proven efficacious in mast cell–mediated experimental models of acute and neurogenic inflammation.[95] It has neuroprotective effects in spinal cord trauma, delayed postglutamate excitotoxic neuron death, and amyloid β-peptide-induced learning and memory impairment in mice.[46] It reduces brain edema from ischemia and hemorrhage by blocking mast cell activation in animals.[96,97]

Palmitoylethanolamide modulates glutamate neurotransmission. The glutamate receptor, *N*-methyl-D-aspartate (NMDA), is upregulated in the median prefrontal lobe in animals subject to neuropathic injury. This upregulation in the prefrontal lobe may be responsible not only for pain but also for anxiety and depression commonly observed with neuropathic pain.[98-100] *N*-methyl-D-aspartate receptors in pre- and postlimbic areas cause neuroplasticity that leads to chronic neuropathic pain.[101] Palmitoylethanolamide is increased in the median prefrontal cortex in neuropathically injured animals and reduces NMDA neurotransmission.[102] Glutamate causes synaptic modification in the medial prefrontal lobe with injury characterized by changes in density proteins and amino acid levels. Increased PEA levels in the region cause a resolution of pain and depressive-like syndrome in selective nerve injured mice. Palmitoylethanolamide restores glutamatergic synapse proteins and changes in amino acid release.[102] Palmitoylethanolamide also increases NR23 subunits of the metabiotic glutamate receptor 3, which modulates glutamate neurotransmission and may be an additional mechanism for antinociception in animals.[102]

Palmitoylethanolamide increases serotonergic neurotransmission through the serotonin receptor 5HT1 and downregulates 5HT2A/C receptors. CB1 agonists are reported to reduce the reuptake of dopamine and serotonin.[103,104] Deletions of CB1 receptors in animals reduce synaptic serotonin caused by selective serotonin reuptake inhibitors.[105] This appears to be an entourage effect by delaying AEA metabolism through FAAH.[106-109] Blocking CB1 receptors produces depression in animals. Clinical depression leads to the removal of the CB1 antagonist rimonabant from the market.[110-112] Conventional antidepressants such as fluoxetine increase CB1 receptor density in prefrontal lobes of treated animals, which could be targeted by CB1 agonists or by entourage effects of PEA.[113]

Palmitoylethanolamide is an uncompetitive inhibitor of CNS butylcholinesterase.[114] Butylcholinesterase knockout mice have reduced fibrillar A-β proteins and are protected from Alzheimer disease.[115,116]

Potential Uses and Clinical Studies of PEA

Pain

Neuropathic pain—Animals. Palmitoylethanolamide in animal models reduces pain behaviors from neuropathic injury resulting from chemotherapy. These studies also demonstrate objective improvements in nerve function.[117,118] Palmitoylethanolamide

prevents oxaliplatin hypersensitivity, allodynia, reduced cyclooxygenase 2 expression, spontaneous neuron depolarization, and evoked spinal cord activity in rats.[118] It reduces paclitaxel pain behaviors and potentiates gabapentin antinociception in mice.[66] Minocycline upregulates PEA production in the ipsilateral spinal as a mechanism of analgesia to selective nerve injury.[119] Mice with chronic constrictive injury to sciatic nerves have reduced hyperalgesia with PEA. The mechanism appears to be activation of PPAR-α and the entourage effect on CB1 receptors.[74] Rats made diabetic through exposure to streptozocin develop neuropathy and hypersensitivity. The combination of PEA plus acetaminophen reduces evoked pain better than either agent alone.[120] Tramadol plus PEA synergistically reduces pain from formalin injections in mice. Analgesia in this model was derived through opioid, PPAR-α, TRPV1 receptors, and ion channel interactions.[121] Cognitive impairment accompanies mice subject to spared nerve injury. Palmitoylethanolamide not only reverses mechanical and thermal allodynia from injury but improves memory deficits. The benefits are dependent on PPAR-α receptors.[122] Objectively, PEA reduces myelin loss from sciatic nerve injury, maintains neuron cell diameters, and reduces nerve edema and macrophage infiltrate that is associated with reduced hypersensitivity. Mice null for PPAR-α fail to respond to PEA.[6]

Neuropathic pain—Humans. Palmitoylethanolamide accumulates in painful tissues in humans. This was seen in trapezius muscle of women with chronic neck pain.[123] Palmitoylethanolamide blood levels also increase in pain processing disorders such as fibromyalgia and in individuals with widespread pain.[124,125]

There have been multiple prospective observational and randomized PEA trials that have been largely used as an add-on analgesic nutraceutical (Table 1). We found 19 studies and 5 randomized controlled trials (RCTs). Trial quality was mixed with little information regarding allocation, randomization procedures, blinding, and attrition. However, PEA reduced painful diabetic neuropathy, neuropathy from chemotherapy, pain from idiopathic axonal neuropathy, nonspecific neuropathy, and pain from sciatic and lumbosacral spine disease. Palmitoylethanolamide, however, failed to improve pain from spinal cord injury in 1 RCT.[133] Palmitoylethanolamide improves pregabalin, oxycodone, and codeine analgesia. Multiple studies of PEA in carpal tunnel syndrome demonstrate improvement in symptoms and objective improvement in nerve function (Table 2).

Visceral pain—Animal studies. There are sparse data regarding PEA benefits to visceral pain relative to neuropathic pain. There are negative studies. For instance, AEA, but not PEA, reduced viscerovisceral responses to turpentine cystitis in animals.[149] However, PEA has had some beneficial effects on gastrointestinal signs and symptoms. Palmitoylethanolamide reduced enteric glia responses and diarrhea related to HIV-1 Tat proteins in rats.[150] In vitro using both Coco-2 colon cell lines and human colon explants, the combination of cannabidiol (CBD) and PEA reduced reactive inflammatory cytokine production, CBD through CB2 receptors and PEA through PPAR-α receptors.[151] Dinitrobenzenesulfonic acid is often used to induce colitis in mice. Palmitoylethanolamide reduced inflammation and reduced colonic permeability in this colitis model. Palmitoylethanolamide stimulates mucosal cell proliferation and increases colonic expression of TRPV1 and CB1 receptors. It benefits in colitis require the presence of GPR55, PPAR-α, and CB2 receptors.[86] It also reduced intestinal permeability caused by interferon-γ and TNF-α. The PPAR-α receptors are the important receptors mediating these benefits. N-acyl acid amidase inhibition increases PEA levels in the colon, which reduces colon inflammation and systemic inflammation in 2 mice models of colitis.[152] Enteric glia activation amplifies intestinal inflammation via the enteroglial-specific S100B protein. In mouse models of dextran sodium sulfate–induced colitis and colonic biopsies derived from patients with ulcerative colitis, PEA improved macroscopic colitis and decreased the expression and release of all pro-inflammatory markers. This was mediated by the selective targeting of the S100B/Toll-like receptor-4.[57]

Visceral—Human studies. Intestinal PEA levels are on average 1.8-fold greater in individuals with ulcerative colitis compared with healthy controls.[153] Intestinal PEA levels are increased 2-fold during active celiac disease and return to normal with remission.[154] Liver and hepatic vein PEA levels are significantly elevated in cirrhosis, more than AEA.[155] Palmitoylethanolamide is increased in patients with pain from pancreatitis and pancreatic cancer.[156] In a small series of patients with colonic inertia, FAAH enteric neuron expression was found to be reduced, CB1 receptor expression on enteric ganglions was also reduced, and intestinal PEA, AEA, and 2-AG levels were increased.[157] These findings reflect either an entourage effect of PEA or a direct effect of AEA and 2-AG on CB1 receptors and motility. Overall, PEA appears to be upregulated in multiple visceral inflammatory and painful diseases.

There are no studies of PEA in the treatment of colitis that we could find. There is one study centered on irritable bowel syndrome reviewed in Table 3 with symptom improvement.[161] Most studies involving visceral pain include women with chronic pain syndromes, the majority of which are due to endometriosis (Table 4). Most clinical studies combined PEA with transpolydatin, which is a stilbenoid glucoside of resveratrol. This agent becomes trans-resveratrol and transversatrol-3-O-glucuronide in the small bowel, which leads to much higher (1000-fold) blood and tissue levels of resveratrol. Resveratrol increases PEA levels in the CNS and increases PPAR-α as well as CB1 and CB2 receptors expression.[173,174] The combination of PEA with transpolydatin significantly reduced pain, dysmenorrhea, and dyspareunia associated with endometriosis in multiple studies.

Other pain syndromes—Animal studies. Intracerebroventricular PEA reduces peripherally (paw) injected carrageenan inflammatory pain in mice through activation of PPAR-α receptors.

Table 1. Palmitoylethanolamide Neuropathic Pain Trials.

Study	Design/Number of Participants	PEA Dose/Time Frame	Comparator	Outcomes	Results	Adverse Effects
Schifilliti et al[126]	Observational, pre-/postintervention, N = 30, diabetic neuropathy	mPEA, 600 mg/d, 60 days	–	Michigan Neuropathic Screening Instrument, Total Symptom Score, Neuropathic Pain Symptom Inventory	Reduced pain severity ($P < .0001$), reduction in related symptoms ($P < .0001$)	No SAE
Desio et al[127]	Observational, N = 30, neuropathic pain unresponsive to pregabalin	umPEA, 1200 mg/d with pregabalin, 45 days	–	VAS (0-10)	With the addition of umPEA VAS 7 to 1.3	
Biasiotta et al[128]	Observational, N = 30, neuropathic pain	PEA, 600 mg/d, added on to analgesics	–	Neurophysiologic parameters, pain severity	Improved laser-evoked potentials in the hands and feet, reduced pain severity	
Truini et al[129]	Observational, N = 20, chemotherapy-related neuropathy (thalidomide and bortezomib)	PEA, 600 mg/d	–	Neurophysiologic studies, pain, Douleur Neuropathique 4 (DN4) scale, motor and sensory fiber function	Improved laser-evoked potentials, improved A-α, A-β, A-δ fiber function ($P < .05$)	
Cocito et al[130]	Observational, N = 30, chronic neuropathic pain, DN4 scale score >4 and VAS (0-10) >6	umPEA, 1200 mg/d, 40 days	–	VAS, Neuropathic Pain Symptom Inventory, Health Questionnaire 5 dimensions (EQ-5D)	VAS 8.2 to 6.4 at day 10 ($P < .002$), 8.2 to 5.8 on day 40 ($P < .001$) NPSI improves from 5.2 to 3.8 on day 40 ($P = .025$), EQ-5D improves from -0.36 to $+0.5$ ($P < .001$)	
Semprini et al[131]	Observational N = 25, diabetic neuropathy, reduced mean nerve conduction time	PEA, 1200 mg/d, 16 weeks	–	Nerve conduction studies, VAS	Increased conduction amplitude and reduced pain	
Hesselink et al[132]	Case series, N = 7, neuropathic pain, chronic idiopathic axonal polyneuropathy refractory to standard analgesics	mPEA, 1200 mg/d, various time periods starting from day 14, add-on to analgesics	–	Pain severity	30% to 50% reduction in pain intensity over 2 to 3 weeks	
Hesselink et al[8]	Case series, N = 7, various neuropathies on analgesics	mPEA, 1200 mg sublingual for 10 days, then 1200 mg by mouth	–	NRS for pain intensity	40% to 80% reduction in pain intensity over 2 weeks	Mild diarrhea and stomach upset in 1 to 2 patients
Andresen et al[133]	RCT, N = 73, neuropathic pain from spinal cord injury, add-on to analgesics	umPEA, 1200 mg sublingual/d, 12 weeks	Placebo	NRS (0-10) Average intensity weeks 2 to 12 Daily spasticity modified Tardieu Muscle stiffness Rescue analgesics Pain descriptors Impact of neuropathic pain QoL using Pain Survey, Insomnia by the Insomnia Severity Index, Major Depression Inventory, number needed to treat, general anxiety disorder	No difference in the primary outcome (NRS), reduced rescue medications with PEA, increased subjective but not objective spasticity with PEA, no difference in other outcomes	No difference in SAE
Guida et al[134]	RCT, N = 636, chronic sciatic pain	PEA, 300 mg/d, 600 mg/d	Placebo	VAS pain severity	VAS 6.5 to 4.5 on placebo, VAS 6.5 to 3.5 on 300 mg/d, VAS 7.1 to 2.1 on 600 mg/d ($P < .05$)	No AE

(continued)

Table 1. (continued)

Study	Design/Number of Participants	PEA Dose/Time Frame	Comparator	Outcomes	Results	Adverse Effects
Desio et al[135]	Observational, N = 30, chronic low-back pain not responding to analgesics	PEA, 100 mg/d plus oxycodone 5 to 25 mg/d, 30 days	–	VAS pain	VAS 7 to 2.5	No AE
Canteri et al[136]	RCT, N = 111, lumbosacral spine pain with a neuropathic component	PEA, 300 mg/d, 600 mg/d, ±NSAID	Placebo	VAS pain	VAS 9 to 6 on placebo, VAS 9 to 3.5 on 300 mg/d, VAS 9 to 1.5 on 600 mg/d ($P < .05$)	No AE
Palomba et al[137]	RCT, N = 81, open comparison, chronic low-back pain on gabapentin, tricyclic antidepressants, or duloxetine	PEA, 1200 mg for 21 days, then 600 mg for 51 days	Standard analgesics	VAS pain	Less pain than standard ($P < .05$)	No AE
Dominguez et al[138]	Observational, N = 85, lumbosciatic pain	PEA, 600 mg/d	"Usual care"	Pain reduction by VAS	Usual care pain reduction by 2.69, with PEA 3.85 ($P < .05$)	No AE
Dominquez et al[139]	RCT, N = 118, neuropathic pain from lumbosciatica	PEA, 600 mg/d plus standard therapy	Standard therapy	VAS pain, Oswestry Disability Index, S-12 Health Survey	VAS and the 2 physical components of the SF-12 improved relative to standard care	
Passavanti et al[140]	Observational, N = 55, chronic low-back pain with a neuropathic component by DN4 > 4	umPEA, 1200 mg/d, 6 months plus tapentadol 100 500 mg/d	Retrospective on tapentadol alone,100-500 mg/d, 6 months	VAS pain, DN4, Oswestry Disability Index (ODI)	VAS on tapentadol 7.7 to 5.9, PEA 7.4 to 4.5 ($P < .0001$) DN4 6.1 to 5.0 on tapentadol, PEA 6.1 to 3.2 ($P < .0001$), ODI on tapentadol 54.6 to 44.6, PEA 56.9 to 37.7 ($P < .0012$)	Diarrhea in 15% of PEA group
Paladini et al[141]	Observational, N = 35, failed back surgery	umPEA, 1200 mg for 1 month, then 600 mg the second month while on tapentadol 150 mg/d and pregabalin 300 mg/d	Tapentadol 150 mg and pregabalin 300 mg 3 month prior to starting PEA	VAS pain severity	Tapentadol/pregabalin, VAS 5.7 to 4.3, added PEA 4.3 to 1.7 ($P < .0001$)	
Morera et al[142]	Observational, N = 112, lumbosciatic pain	PEA	–	SF-12 QoL	Improved mental health better in men than woman	
Chirchiglia et al[143]	Observational, N = 155, nonsurgical lumbar radiculopathy	Acetaminophen/codeine 500/30 for 7 days, then switched to umPEA 1200 mg/d for 30 days; if no response, then addition PEA 600 mg for 30 days followed by 30 days of acetaminophen plus codeine	–	VAS pain severity	First cycle those with mild pain (3-4) responded to 1, those with moderate pain (5-6) responded to 2 (75%), second cycle, all moderate pain responded, but 26% of severity pain did not respond	

Abbreviations: AE, Adverse effects; mPEA, micronized palmitoylethanolamide; NRS, Numerical rating scale; NSAID, nonsteroidol anti-inflammatory drug; QoL, quality of life; RCT, randomized controlled trials; SAE, Serious, adverse effects; umPEA, ultramicronized palmitoylethanolamide; VAS, Visual Analog Scale.

Table 2. Palmitoylethanolamide in Entrapment Neuropathies.

Study	Design/Numbers	PEA/Time Frame	Comparator	Outcomes	Results	Adverse Effects
Evangelista et al[144]	RCT, open label, N = 42, patients with CTS	umPEA, 1200 mg/d, pre- and postsurgery	Standard care without PEA	Sleep quality by PSQI, NRS pain intensity	Sleep quality improved ($P < .000$), increased total sleep time, reduced latency, reduced pain ($P < .0001$)	
Coraci et al[145]	RCT, N = 56, mild to moderate CTS	PEA, 600 mg/d for 30 days	Placebo	Sensory nerve conduction velocity, distal motor latency, compound action potential, US cross section of median nerve	Sensory conduction was improved with PEA, increased cross section of median nerve with PEA, pilot and underpowered for significance	
Faig-Marti et al[146]	RCT, N = 68, mild to moderate CTS	PEA, 600 mg/d for 60 days	Placebo	ENG, Levine questionnaire, Symptom Severity Scale, Durkin test, Phalen test, Boston Questionnaire	No improvement in clinical or ENG parameters, improvement in the Boston Questionnaire FSS subscale with PEA	
Conigliaro et al[147]	RCT, N = 26, moderate CTS	PEA, 600 mg/d, 1200 mg/d for 30 days	Standard care	Median nerve latency, Tinel sign, pain	PEA improved median nerve latency ($P < .0004$), improved pain and Tinel sign. Placebo VAS pain 5.4 to 5.4, PEA 600 mg/d; VAS 6.6 to 4.8, PEA 1200 mg/d; VAS 6.0 to 3.9 ($P < .0005$)	
Assini et al[148]	RCT, N = 40, diabetics with CTS and a VAS of 7 to 8	PEA, 1200 mg/d	Placebo	VAS ENG	PEA improved pain ($P < .0001$), improved sensory action potentials, sensory conduction velocity, and median nerve latency	No AE

Abbreviations: AE, Adverse effects; CTS, carpal tunnel syndrome; ENG, electroneurogram; mPEA, micronized palmitoylethanolamide; NRS, Numerical rating scale; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trials; umPEA, ultramicronized palmitoylethanolamide; US, ultrasound; VAS, Visual Analog Scale.

Palmitoylethanolamide reduces cyclooxygenase 2 and inducible nitric oxide synthase and increases PPAR-α expression in sciatic nerves and L4-6 dorsal root ganglion. Palmitoylethanolamide prevents Iκ-B degradation and translocation of NF-κB nuclear translocation.[54] Certain nonsteroidol anti-inflammatory drugs, such as nimesulide, increase tissue PEA levels by blocking catabolism of PEA.[45] Palmitoylethanolamide reduces formalin-induced pain at intraperitoneal doses that produce no increase in circulating PEA levels in mice.[9] Palmitoylethanolamide reduces hyperalgesic responses to complete Freund adjuvant.[9] Spinal allopregnanolone levels are increased by PEA both in formalin- and carrageenan-exposed mice, which is associated with reduction in pain.[63] Palmitoylethanolamide reduces tibial fracture pain in rodents and increases fracture healing.[175] Palmitoylethanolamide prevents arthritis in rodents caused by injections of bovine collagen II.[176] It reduces mechanical and thermal hyperalgesia and macrophage infiltrate into the temporomandibular joint caused by injections of complete Freund adjuvant in rats.[177]

Other pain syndromes—Human studies. Palmitoylethanolamide is an effective analgesic or adjuvant analgesic in a multitude of pain syndromes. Circulating PEA levels are increased in the burning mouth syndrome.[178] Palmitoylethanolamide levels in synovial tissues at the time of total knee replacement correlate with disability, but not with pain severity.[179] In 2 meta-analyses, PEA has significant analgesia either as a single agent or as an add-on analgesic in multiple pains.[11,12] In one meta-analyses, the weighted mean differences between PEA and inactive comparator (placebo or equivalent) were remarkably high, indicating a very large effect size.[11] However, the analyses involved a small number of studies with significant potential biases. Palmitoylethanolamide responses in trials with active controls were also significantly different with a large effect size difference. Palmitoylethanolamide was effective in reducing pain from fibromyalgia, burning mouth syndrome, temporomandibular joint disease, and molar extractions.

Neurodegenerative and Neuropsychiatric Disorders

Strokes and Ischemic–Reperfusion Injury—Animal Studies

Palmitoylethanolamide reduces infarct size, neuron loss, and improves motor behaviors in Wistar rats after ischemic–reperfusion cerebral injury.[16] Palmitoylethanolamide prevents neuroinflammatory responses to brain anoxic injury, reduces

Table 3. Palmitoylethanolamide in Miscellaneous Pain Phenotypes.

Study	Design/Number	PEA/Time Frame	Comparator	Outcomes	Results	Adverse Effects
Paladini et al[144]	Meta-analysis, N = 12 studies, 3 RCTs, N = 1485 patients, multiple phenotypes, 2010-2014	mPEA or umPEA, 300-1200 mg/d for 60 days, add-on to analgesics	In RCT placebo or active comparator	VAS pain severity	Pain severity reduced at 2 weeks with placebo decreased by 0.2 with PEA 1.04 ($P < .001$) VAS pain severity at 60 days placebo 6.6 to 6.6, VAS pain with PEA 6.6 to 2.9, VAS $\leq$3/10 placebo 41%, PEA 82%	
Artukoglu et al[145]	Meta-analysis, N = 10 RCT, N = 1289 patients, multiple pain phenotypes	PEA, 300 to 1200 mg/d, 14 to 180 days	Active and inactive controls	VAS pain severity	PEA >placebo with WMD 2.03 ($P < .001$), no difference if blinded or open-label study, active controls PEA >control WMD 1.31 ($P < .005$), no association of benefits to duration of therapy	Attrition PEA 1.1%, comparator 4.3%
Del Giorno et al[158]	Observational, retrospective/prospective, N = 80, fibromyalgia on duloxetine plus pregabalin at low doses (39 mg, 47 mg/d) for 6 months	umPEA, 1200 mg/d for 30 days, then 600 mg/d for 60 days	Duloxetine plus pregabalin alone for 6 months	VAS pain severity. Number of tender points (TP)	On duloxetine plus pregabalin, TP 14/18 to 8/18, VAS 6.9 to 4.0 at 3 months, TP at 6 months 4/18, and VAS 3.0, prospective study, addition of PEA at 3 months reduced TP 1/18 and VAS 1.9 ($P < .0001$)	No AE
Ottaviani et al[159]	RCT, N = 35, burning mouth syndrome, NRS >5	umPEA, 1200 mg/d for 60 days	Placebo	NRS pain severity	Reduced sensation ($P < .0132$)	No AE
Marini et al[160]	RCT, N = 24, temporomandibular joint osteoarthritis	PEA, 900 mg/d for 7 days, then 600 mg/d for 7 days	Ibuprofen 600 mg 3 times daily for 2 weeks	VAS pain severity, maximum mouth opening	VAS pain severity reduction PEA >ibuprofen ($P = .0001$), maximum mouth opening PEA >ibuprofen ($P = .022$)	
Cremon et al[161]	RCT, N = 54, irritable bowel syndrome (IBS) by Rome III criteria	umPEA/transpolydatin, 400/40 mg/d for 12 weeks	Placebo	Symptom scale for flatulence, abdominal pain/discomfort, dyspepsia changes and frequency of stool, Bristol Stool Scale, GI immunohistochemistry, mast cell quantification, mucosal endocannabinoids, TRPV1, CB receptors	Mast cells increased in IBS not changed with treatment, no change in histochemistry with treatment, OEA reduced and CB2 receptors increased in IBS, PEA reduced pain ($P = .049$), PEA responders 62% versus placebo 40% ($P = .115$)	No AE
Gatti et al[162]	Observational, N = 610, chronic pain (pain >6 months, except herpes zoster), various phenotypes, NRS >4	umPEA, 1200 mg/d for 3 weeks, then 600 mg/d for 4 weeks added to analgesics, in 95, PEA was the only analgesic	–	NRS pain severity	NRS 6.4 to 2.4 ($P = .001$), unrelated to pain phenotype, age, or gender, PEA alone 6.5 to 2.4 ($P < .0001$), NRS improvement better if PEA is started early in herpes zoster ($P = .0183$)	
Phan et al[163]	Observational, N = 8, herpes zoster of the face	Topical PEA	–	VAS pain severity	5 of 8 had a mean reduction of 88% of their pain	Therapy well tolerated
Bacci et al[164]	RCT, N = 30, third molar extraction, split mouth randomization (patient own control)	umPEA, 800 mg/d for 15 days	Placebo	VAS pain severity Facial swelling Trismus NSAID consumption Complications Tolerability	VAS improved with PEA >placebo 3.8 versus 5.5 as day 7, 1.0 versus 1.5 day 15 ($P < .0221$), Trismus the same between PEA and placebo, edema same between groups	One patient had palpitation and 1 drowsiness on PEA

Abbreviations: CB, cannabinoid, GI, gastrointestinal; mPEA, micronized palmitoylethanolamide; NRS, Numerical rating scale; NSAID, nonsteroidol anti-inflammatory drug; OEA, oleoyl ethanolamine; RCT, randomized controlled trials; TRPV1, transient receptor potential vanilloid-1; umPEA, ultramicronized palmitoylethanolamide; VAS, Visual Analog Scale; WMD, weighted mean difference.

Table 4. Palmitoylethanolamide and Pelvic Pain Syndromes.

Study	Design/Numbers	PEA/Time Frame	Comparator	Outcome	Results	Adverse Effects
Tartaglia et al[166]	RCT, N = 220, primary dysmenorrhea in adolescents and young women	mPEA/transpolydatin, 400/40 for 10 days beginning the 24th day of the menstrual cycle	Placebo	VAS pelvic pain	Improved pain PEA 98.2% versus 56.4%, mean improvement with PEA 4 points versus 1 point ($P < .001$)	
Indraccolo et al[165]	Observational, N = 4, endometriosis	mPEA/transpolydatin, 400/40 mg/d for 90 days	–	VAS pain severity	Pain reduced from 77 to 31 mm ($P < .0069$), improved dyspareunia, and reduced analgesic use	One patient had nausea
Lo Monte et al[167]	Observational, N = 24, severe pelvic pain from endometriosis	mPEA/transpolydatin, 800/80/d for 90 days	–	Pain, dysmenorrhea, dyspareunia, dyschezia, QoL	Decreased pain, dysmenorrhea, dyspareunia, improved QoL $P < .05$), decreased NSAID use	
Giugliano et al[168]	Observational, N = 47, pain from endometriosis on 6 months of hormone therapy	mPEA/transpolydatin, 400/40 mg/d for 90 days	–	VAS pain severity, dysmenorrhea, dyspareunia, dyschezia	VAS pain 5.6-2.2, dysmenorrhea, VAS 6.8-4.1, dyspareunia, VAS 6.9-3.2 ($P < .05$)	
Caruso et al[169]	Observational, N = 56, pain from endometriosis	mPEA/lipoic acid, 600/600 mg/d, 90 days	–	VAS pain severity, Female Sexual Distress Scale, SF-36	Pain improved ($P < .001$), QoL, improved ($P <.001$), sexual function improved ($P < .001$)	
Giammusso et al[170]	RCT, N = 44, chronic pelvic pain or prostatitis	mPEA/lipoic, 300/300 mg/d, 12 weeks	Serenoa Repens 320 mg/d	NIH-CPSI and IIEF questionnaire	PEA improved the NIH-CPSI score, not IIEF5 score	No AE
Corbellis et al[171]	RCT, N = 61, pain from endometriosis	mPEA/transpolydatin, 800/80 mg/d, 90 days	Placebo for 90 days, celecoxib 400 mg/d for 7 days	VAS pain severity, dysmenorrhea, dyspareunia	PEA >placebo ($P < 01$), celecoxib >PEA ($P < .001$)	
Indraccolo et al[172]	Meta-analyses, N = 4 trials, N = 81 patients	mPEA/transpolydatin, 800/80 mg/d, 90 days	–	VAS pain severity, dysmenorrhea, dyspareunia	VAS pain reduced by 4.1, VAS for dysmenorrhea by 3.68, dyspareunia by 3.18 ($P < .001$)	

Abbreviations: IIEF, International Index of Erectile Function; mPEA, micronized palmitoylethanolamide; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; NSAID, nonsteroidol anti-inflammatory drug; RCT, randomized controlled trials; umPEA, ultramicronized palmitoylethanolamide; QoL, Quality of Life; VAS, Visual Analog Scale.

astrogliosis, and preserves cognitive function.[180] It exerts neuroprotective effects on cultured cortical neurons in newborn rats subjected to hypoxic episodes. These protective effects were not mediated by PPAR α receptors or TRPV1.[181] In many of these studies, luteolin was added to PEA. Luteolin is an antioxidant flavonoid that downmodulates neuroinflammation. Luteolin is neuroprotective, improves memory, and reduces anxiety in animal models. Palmitoylethanolamide administered before an experimental ischemic episode and with traumatic brain injury reduces infarct size and neurologic deficits.[182] The combination of PEA and luteolin works in several animal studies where each agent alone did not work. There is, however, no clinical evidence that the combination is better than PEA alone.[2,94,176,183-185] The mechanism of action remains unknown. It is known that it does not depend on the usual PEA targets, such as TRPV1 and or PPAR-α.[186] One mechanism may be by way of reduction in adhesive molecules, thus reducing vascular occlusion.[187]

Strokes—Human Studies

Patients undergoing CNS microdialysis after a stroke had increased NAE in the area of stroke, including PEA that is also increased in surrounding brain tissue.[16,188] Circulating blood levels of PEA at the time of a stroke correlate with the degree of neurological deficits.[189] In an observational study, PEA improved cognitive function, spasticity, and disabilities from a stroke.[16]

Dementia and Alzheimer Disease—Animal Studies

There is a large amount of animal studies using PEA in Alzheimer disease models, but no clinical studies that we could find. In the 3xTg-AD animal model, PEA improved context learning and memory and reduced depression behaviors as well as anhedonia (sucrose preference test).[190] Palmitoylethanolamide reduces the expression of amyloid protein (AB1-42) and prevents τ protein phosphorylation. The NF-κB expression is reduced, as well as inflammatory cytokines. Astrogliosis is curtailed.[190-192] The combination of PEA plus luteolin reduces inducible nitric oxide synthase expression, astrocyte activation, and neuron loss in organotypic hippocampal slices exposed to AB1-42. In addition, PEA upregulates brain-derived neurotrophic factor (BDNF).[193] Serum amyloid protein increases in axon myelin in Alzheimer disease and multiple sclerosis (MS). Palmitoylethanolamide plus luteolin reduces serum amyloid expression.[194] Dysfunctional endocannabinoid systems could play a role in Alzheimer disease.[195,196]

Multiple Sclerosis—Animal Studies

Palmitoylethanolamide reduces motor disabilities in mice models of MS.[197] Exogenously administered endocannabinoids and PEA ameliorate spasticity in chronic relapsing experimental autoimmune encephalomyelitis.[198] Cannabidiol and PEA diminished inflammation, demyelination, axonal damage, and inflammatory cytokine expression, while concurrent administration of CBD and PEA was not as effective in induced experimental autoimmune encephalomyelitis.[199] Flurbiprofen blocks endocannabinoid metabolism centrally and reduces autoimmune encephalomyelitis in mice.[200] Fatty acid amide hydrolase inhibitors do the same and reduce spasticity in mouse autoimmune encephalomyelitis.[201]

Multiple Sclerosis—Human Studies

Circulating PEA levels are reported in 2 MS studies. In one study, circulating levels were increased in secondary progressive MS, while a second found levels increased in both secondary progressive and relapsing remitting MS.[202] Significantly reduced levels of all the tested endocannabinoids were found in the cerebrospinal fluid (CSF) of patients with MS compared to control patients, with lower levels detected in the secondary progressive subtype. Higher levels of AEA and PEA, although below those of controls, were found in the CSF of relapsing remitting patients during relapse.[203] Circulating endocannabinoids can arise from vascular endothelium, platelets, and monocytes or may reflect an impaired blood–brain barrier with leakage of PEA from CNS such that circulating levels may not reflect disease state of the CNS.[204,205] A small study reported only as an abstract demonstrated improved pain in 14 of 20 patients treated with 300 mg of PEA twice daily (Table 5).

Parkinson Disease—Animal Studies

Palmitoylethanolamide improves dopamine neurotransmission and restores tyrosine hydroxylase activity within the substantia niger in a mouse model of PD.[208,209] In a model of PD in which injury was induced by the dopaminergic toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), intraperitoneal injections of PEA prevented Parkinsonian behaviors, maintained the expression of tyrosine hydroxylase reduced by MPTP, and blunted the upregulation of α-synuclein that is associated with PD.[210] The combination of PEA plus luteolin blocks both the neuroinflammation and the autophagic pathway involved in PD in mice.[211]

Parkinson Disease—Clinical Studies

The addition of ultramicronized PEA to patients with PD receiving levodopa therapy significantly and progressively reduced the revised Movement Disorder Society/Unified Parkinson Disease Rating Scale questionnaire score over 1 year (Table 5). For each item, the mean scores between baseline and end of treatment were significantly reduced for most nonmotor and motor symptoms.[15]

Autism—Animal Studies

BTBR T+tf/J mice develop autistic behavior; PEA reversed autistic behaviors in mice. This effect was contingent on activation of PPAR-α receptors. Palmitoylethanolamide restored

Table 5. Palmitoylethanolamide in Neuropsychological and Neurodegenerative Disorders.

Study	Design/Numbers	PEA/Time Frame	Comparator	Outcome	Results	Adverse Effects
Ghazizadeh-Hashemi et al[13]	RCT, N = 58, major depressive disorder, Hamilton Rating Scale for Depression- 17 (HAMD) >19	umPEA, 1200 mg/d for 6 weeks plus citalopram 40 mg/d	Citalopram 40 mg/d plus Placebo	HAMD at 2, 4, 6 weeks Response (50% reduction in HAMD), remission HAMD <8	HAMD at 2 weeks PEA >placebo, reduced 8.3 versus 5.8 ($P = .004$), 6 weeks PEA >placebo in reduced depression symptoms ($P = .021$), response rate >PEA ($P = .01$)	No AE
Khalaj et al[14]	RCT, N = 70, autism, ages 4-12, Aberrant Behavior Checklist–Community (ABC-C) >12	PEA, 1200 mg/d plus risperidone for 10 weeks	Risperidone plus placebo	ABC-C Adverse effects	PEA >placebo irritability ($P = .002$) and hyperactivity ($P < .001$), inappropriate speech ($P = .05$)	No AE
Antonucci et al[206]	Two case report, autism ages 13 and 15	umPEA, 600 mg/d	–	Childhood Autism Rating Scale	Improved socialization, language, improved cognition, reduced aggression	No AE
Brotini et al[15]	Observational, N = 30, Parkinson disease on levodopa	umPEA, 600 mg/d for 1 year	–	Revised Movement Disorder Society/ Unified Parkinson Disease Rating Scale	Significant improvement in motor and nonmotor symptoms. Motor total score decreased from 43 to 23 including speech ($P = .012$) and walking and balance ($P = .0004$), nonmotor symptoms improved, particularly mood, sleep, and fatigue ($P < .005$)	No AE
Orefice et al[207]	RCT, N = 29, multiple sclerosis relapsing remitting subtype on interferon-1β for 6 months	umPEA, 600 mg/d for 12 months	Placebo	Expanded Disability Status Scale, Multiple Sclerosis Quality of Life Scale-54, Paced Auditory Serial Addition Test, VAS pain severity, endocannabinoid blood levels, cytokine levels	PEA improved pain with interferon, improved cognitive function with PEA and QoL, no change in serial addition, no change in disease course, reduced interferon-γ, TNF-α, and IL-17 with PEA, slight increase in expression of FAAH in placebo, inverse relationship between interferon-γ and PEA	No AE
Caltagirone et al[16]	Observational, N = 267, individuals with first stroke, stabilized and in rehabilitation	umPEA/luteolin, 1400/140 mg/d sublingual for 60 days	–	Canadian Neurological Scale, MMSE, Ashworth Scale for spasticity, NRS pain severity, Barthel Index for disability	Improved Canadian Neurological Scale ($P = .0049$), improved MMSE ($P < .0001$), improved spasticity ($P < .0075$), improved pain ($P = .0014$), improved disabilities and activities of daily living ($P < .001$)	No AE

Abbreviations: IL-17, interleukin 17; MMSE, Mini-Mental Status Examination; mPEA, micronized palmitoylethanolamide; RCT, randomized controlled trials; TNF-α, tumor necrosis factor α; umPEA, ultramicronized palmitoylethanolamide; VAS, Visual Analog Scale.

hippocampal BDNF signaling pathways and improved mitochondrial dysfunction, both known to be consistently associated with autism.[212] Additional evidence supporting PPAR-α as the important receptor target in autism comes from a study using valproic acid. Valproic acid produces autistic behavior in rats, which is directly associated with the reduction in expression of PPAR-α receptors.[213]

Autism—Clinical Studies

There are 2 case reports and a small randomized trial of PEA in the management of autism.[14,183,206] A randomized trial of 70 children with moderate to severe autism by the Aberrant Behavior Checklist–Community Edition randomized children to risperidone with or without PEA. Palmitoylethanolamide significantly improved the therapeutic effects of risperidone on irritability and hyperactivity (Table 5).[14]

Seizures—Animal Studies

There is a modest amount of evidence that PEA has on antiseizure activity, though there are no clinical studies. Palmitoylethanolamide reduces tonic convulsions from maximum electroshock and chemical-induced seizures in mice. Efficacy was similar to phenytoin at similar doses (8.9 vs 9.2 mg/kg). The therapeutic index of PEA was much wider since unlike phenytoin, PEA impairment did not occur at doses as high as 250 mg/kg.[214] The actions appear to be similar to the fatty acid valproic acid.[214] Palmitoylethanolamide increased the latency to clonus in rats exposed to amygdala kindling. Palmitoylethanolamide was also effective against pentylenetetrazol-induced convulsions at a dose of 40 mg/kg.[215] In another mouse model, PEA blocked kainic acid chronic seizures and was neuroprotective to ongoing seizures.[216]

Neuropsychiatric Disorders

Depression—Animal Studies

There are multiple animal studies that have demonstrated antidepressant activity. Palmitoylethanolamide reduces depression (immobility) from forced swimming in mice at a dose of 20 mg/kg, which is equivalent to fluoxetine at the same dose.[217] Certain antidepressants increase PEA levels in the brain. Antidepressant withdrawal reduces PEA in critical brain areas (frontal cortex, hippocampus, dorsal striatum).[218] Long-term corticosteroid exposure to 129Sv/Ev mice induces anxiety and depression. Palmitoylethanolamide plus luteolin (1 mg/kg, intraperitoneal) improves depression-like behavior, as assessed by open-field, novelty suppressed feeding, forced swim test, and elevated maze testing. Not only does anxiety and depression improve, but hippocampal neurogenesis and neuroplasticity improve, both of which are usually diminished with depression.[185]

Depression—Clinical Studies

Circulating PEA levels are significantly lower in women who are depressed compared with healthy controls.[219,220] A randomized double-blind trial added 1200 mg/d of PEA or placebo to citalopram in 58 patients (Table 5). The Hamilton Depression Rating Scale was used to measure outcomes at 2, 4, and 6 weeks.[13] Palmitoylethanolamide shows significantly greater improvement in depressive symptoms compared to placebo group throughout the trial period. The response rate defined as a 50% reduction in the Hamilton Depression Rating Scale was 100% for PEA and 74% for placebo at 6 weeks.

Post-Traumatic Stress Disorder—Animal Studies

Post-traumatic stress disorder is characterized by alterations in mood, impaired socialization, and cognition. In animal models of PTSD, CNS PEA and neurosteroids levels are reduced.[65] The FAAH inhibitor SSR411298 exerts anxiolytic-like effects following exposure to a traumatic event, in a mouse defense test battery and social defeat procedure. SSR411298 increases CNS endocannabinoid levels, including PEA in rodents.[221] Another FAAH inhibitor, URB597, increases brain endocannabinoids and reduces acute and chronic stress in rats.[222]

Post-Traumatic Stress Disorder—Clinical Studies

In a study that investigated PTSD-associated differences in human hair endocannabinoids, patients with PTSD had reduced hair concentrations of PEA. Regression analyses demonstrated a strong negative relationship between all investigated NAEs and severity of PTSD.[223] Post-traumatic stress disorder is associated with a significant incidence of suicide, and endocannabinoids and neurosteroid biosynthesis are reduced in suicidal individuals.[65] Paradoxically in individuals with PTSD compared with individuals who sustain trauma but do not develop PTSD, PEA levels were higher in the PTSD group. Clinician Administered PTSD Scale scores correlated positively with circulating PEA levels.[224] There are no observational or randomized trials of PEA in the treatment of PTSD.

Morphine Analgesic Tolerance—Animal Studies

Morphine analgesic tolerance is associated with neuroinflammation and astrogliosis.[225] In rats, PEA significantly attenuates morphine analgesic tolerance and doubles the number of days of morphine antinociceptive. Palmitoylethanolamide prevents morphine-related microglia and astrocyte proliferation in the dorsal horn.[226]

Morphine Analgesia—Clinical Studies

In a randomized study of 42 total knee arthroplasty, patients were given either intrathecal morphine (200 μg) or placebo at the time of the spinal anesthesia. Patients receiving intrathecal morphine had reductions in AEA, PEA, and OEA compared to

placebo.[227] Palmitoylethanolamide improves oxycodone, codeine, and tapentadol analgesia (Table 1).

Discussion

Palmitoylethanolamide is a multifaceted endocannabinoid nutraceutical with intriguing activity, but evidence as to clinical benefits is fragmentary for pain and nonpain symptoms in a number of diseases. Initial interests in PEA were related to influenza A and the management of rheumatic fever, which have largely been ignored over the past 3 decades. Palmitoylethanolamide is best known in the literature as a co-analgesic for neuropathic pain since most studies added PEA to preexisting analgesics, and rarely was it used as a single analgesic. Two recent meta-analyses of trials involving patients with multiple pain syndromes have demonstrated significant analgesic benefits to PEA with very few adverse effects. Palmitoylethanolamide has been used for entrapment neuropathies in a fair number of studies as well as pain from endometriosis. Combinations with luteolin and transpolydatin have been used in a multitude of studies, but there are no randomized comparisons to PEA alone.[176] The same can be said for ultramicronized PEA versus PEA that is not micronized.[228,229] The claim of increased bioavailability has not been correlated with clinical studies in humans.[230]

Palmitoylethanolamide has promising potential but with sparse clinical evidence in the management of several neurodegenerative disorders, such as Alzheimer disease (although there are no clinical trials), PD, autism, MS, and strokes.[14,15,196,198,202,211,231,232] What is fairly remarkable is PEA safety *in* both animal studies and clinically. There are no reported drug–drug interactions. Diarrhea and stomach upset occur rarely.[117]

There are large gaps in our understanding of the pharmacokinetics and clinical pharmacodynamics of PEA. In animal studies, critical targets involve PPAR-α receptors, TRPV1 receptors, GPR55, and the entourage effects involving other endogenous cannabinoids. Which receptor or interaction is responsible for which clinical benefit is not known? Most clinicians are unaware of PEA. There is a need for clinical trials, but this is a nutraceutical and not a medication according to the US Food and Drug Administration so that funding from pharmaceutical companies is unlikely to occur. Pilot studies have been done using N-of-1 study designs, which may be a step forward in advancing clinical trials.[233]

Conclusion

Palmitoylethanolamide is a nutraceutical with a complex pharmacodynamic profile and relatively unknown pharmacokinetics. The palliative benefits for multiple patients are intriguing but require more research.

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