

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Palmitoylethanolamide (PEA)

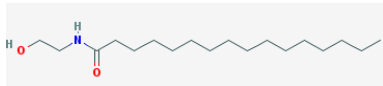
Evidence Summary

PEA has anti-inflammatory effects and reduces pain in people with chronic or neuropathic pain. No studies have tested whether it prevents cognitive aging or dementia.

Neuroprotective Benefit: PEA has strong anti-inflammatory effects in preclinical models, but no studies have tested whether it improves cognitive function in healthy adults.

Aging and related health concerns: Many studies have shown that PEA reduces pain in people with chronic/neuropathic pain, though study qualities were not high.

Safety: Numerous clinical trials have shown that PEA is generally well-tolerated in people with chronic pain and other conditions, though a few adverse events including infection have been reported in some patient populations.

Availability: OTC in capsule, tablet, and powder form	Dose: clinical trials in people with chronic pain have used 600 mg of ultramicrosized PEA twice daily	Chemical formula: C ₁₈ H ₃₇ NO ₂ MW: 299.499 g/mol  Source: PubChem
Half life: 12 hr (based on a study in people with TMJ pain)	BBB: likely penetrant based on preclinical studies	
Clinical trials: largest meta-analysis of RCTs included 786 patients who received PEA	Observational studies: largest observational study included 610 patients with chronic pain	

What is it? Palmitoylethanolamide (PEA) is a fatty acid amide produced in the body that binds to and activates the peroxisome proliferator-activated receptor alpha (PPAR-α). It was initially described as an agonist to the type 2 cannabinoid receptor (CB2), though it is now recognized that PEA does not bind to cannabinoid receptors ([PubChem](#)). PEA is known to have anti-inflammatory, analgesic, and neuroprotective properties. PEA supplements have been used by people with chronic pain as well as those with neuropathic pain.

Neuroprotective Benefit: PEA has strong anti-inflammatory effects in preclinical models, but no studies have tested whether it improves cognitive function in healthy adults.

Types of evidence:

- 1 open-label clinical study in stroke patients
- 2 case studies
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have tested whether PEA prevents dementia or age-related cognitive decline.

One open-label clinical study in 250 stroke patients reported that treatment with co-ultramicrosized PEA (700 mg) + luteolin (a flavonoid, 70 mg) for 60 days significantly improved cognitive function and muscle spasticity [1]. The average MMSE score over 30 days of treatment increased from 20.2 to 22.7.

Patients' independence and mobility in daily living activities showed a significant improvement after 30 and 60 days of treatment. The difference was significant between 30 and 60 days, suggesting continued improvement with time. A major caveat to this study is that it is an open-label study and patients suffering from stroke typically show functional improvement over time.

The only other studies that examined cognitive outcomes with PEA were in autistic boys. In a report of 2 autistic boys (ages 13 and 15), one subject showed significant improvement with 1 month of PEA (Normast®, 600 mg twice daily) treatment in expressive language, where a two-year gain was observed [2]. This subject also had increased vitamin D levels (due to better absorption) and CD57 natural killer cell counts (without a change in total white count). The other boy also improved in cognitive and behavioral skills after 3 months of PEA treatment, though only mild improvements were seen with language. In a more recent case study of a 10-year old boy, co-ultramicrosized PEA-LUT (700 mg PEA + 70 mg luteolin, twice daily; Gliolia®) for 1 year resulted in significantly improved behavioral outcome (by about 23% on an autism scale) with significant progress in cognitive and sociability behavior and the ability to understand and execute simple commands [3]. However, no significant progress with speech was observed.

Human research to suggest benefits to patients with dementia: No studies have tested PEA in patients with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

AD models: Several studies have been carried out in various models of Alzheimer's. Ultramicrosized PEA treatment improved learning and memory in 3xTg AD mice [4], rats infused with A β 42 [5], and mice injected with A β 25-35 [6]. At the highest dose tested (30 mg/kg, s.c.), performance was equivalent to mice injected with scrambled A β 25-35 (not toxic)[6]. In these models, PEA reduces IL-1 β [4], TNF α , hyperphosphorylated tau [5], caspase 3 activation, and lipid peroxidation [6], and increases the anti-inflammatory cytokine IL-10 [4]. Beneficial effects of PEA were not seen in PPAR- α null mice and a synthetic PPAR- α agonist mimicked the positive effects of PEA [6]. In culture models of Alzheimer's, PEA treatment improved neuronal survival by blunting A β 42-induced astrocyte activation and neuroinflammation [7; 8]. However, in one study, PEA displayed protective properties in cultures from non-transgenic mice but not in the 3xTg-AD mice [9]. Reasons for this difference are not known.

TBI model: In a mouse model of traumatic brain injury, co-ultramicrosized PEA-LUT (PEA and luteolin at 1 mg/kg, given 1 hour after injury) significantly decreased edema and brain infarction area and

volume while promoting functional and behavioral recovery [10]. Infarct volume was reduced by 60-70%. Co-ultra-PEA-LUT also prevented the increase in TNF α and IL-1 β to levels comparable to sham-treated mice. This study showed that the combination treatment improved neurobehavioral functions and reduced apoptotic cell death, inflammation, and edema better than PEA alone at the dose of 10 mg/kg.

APOE4 interactions: Unknown.

Aging and related health concerns: Many studies have shown that PEA reduces pain in people with chronic/neuropathic pain, though study qualities were not high.

Types of evidence:

- 3 meta-analyses of clinical studies in people with chronic pain
- 6 clinical trials
- 1 observational study
- 1 biomarker study in people with impaired coronary function
- Numerous laboratory studies

Chronic pain: BENEFIT. Several meta-analyses have examined the effects of PEA on pain. The most recent meta-analysis from 2017 included 10 randomized clinical trials with a total of 786 patients receiving PEA (and 512 controls) [11]. Doses used ranged from 300-1200 mg/day and trial durations ranged from 15-180 days. PEA was associated with a significantly greater pain reduction compared to inactive control conditions (weighted mean difference on a 10-point scale= 2.03, 95% CI: 1.19 - 2.87). Use of placebo control, presence of blinding, allowance for concomitant treatments, and duration or dose of PEA treatment did not affect the measured efficacy of PEA. The overall quality of the clinical studies and assessment of side effects were often poor. For example, 5 out of 10 trials were not blinded and 2 trials did not have a placebo group. Three trials compared PEA vs NSAIDs (celecoxib, ibuprofen) and other medications. Future well-designed, randomized, placebo-controlled trials are needed to provide reliable estimates of its efficacy. In a 2016 meta-analysis that included many of the same studies, the authors noted that clinical studies are of variable quality and while micronized formulations are theoretically more bioavailable, there have not been any head-to-head comparisons between unmiconized vs micronized formulations [12].

In a different 2016 meta-analysis that included 12 clinical studies in people with chronic pain or neuropathic pain, micronized or ultramiconized PEA treatment (mostly 1200 mg/day, Normast®) for

30-365 days elicited a progressive reduction of pain intensity compared to control [13]. A total of 1,188 subjects received either micronized or unmiconized PEA. The magnitude of pain reduction with PEA was 1.04 points every 2 weeks (on a 10-point scale). The control group, on the other hand, only had a reduction of 0.20 points every 2 weeks. This meta-analysis reported that the PEA effects were independent of patient age or gender and also not dependent on the type of chronic pain.

In an observational study of 610 patients with chronic pain of different origins, PEA treatment (1200 mg daily) for 7 weeks significantly decreased the mean score pain intensity from 6-7 down to 2-3, regardless of the underlying condition [14]. PEA-induced decrease in pain intensity was also experienced by patients without concomitant analgesic therapy.

In a small single-blind clinical trial of 44 people with chronic prostatitis or pelvic pain, a combination treatment of PEA (300 mg/day) plus alpha-lipoic acid (ALA; 300 mg/day) (Peanase®) for 12 weeks significantly improved scores on questionnaires when compared to the traditional treatment (Saw palmetto monotherapy, 320 mg/day) [15]. There was no placebo control to this study and it is unclear whether PEA, ALA, or the combination is most effective in reducing pain in this condition.

Neuropathy/Neuropathic Pain: MIXED. In a double-blind randomized controlled trial of 68 people with spinal cord injury-induced neuropathic pain, ultramiconized PEA as add-on therapy (600 mg twice daily, Normast®) for 12 weeks did not decrease pain intensity when compared to placebo [16]. There was also no effect of ultramiconized PEA as add-on therapy on spasticity, insomnia, or psychological functioning.

In contrast, an open-label trial of 30 diabetic patients with neuropathic pain reported that micronized PEA (300 mg twice daily, Normast®) for 60 days significantly reduced pain severity and related symptoms evaluated by the Michigan Neuropathy Screening instrument, Total Symptom Score, and Neuropathic Pain Symptoms Inventory [17]. Because of the open-label design, positive effects may have been exaggerated based on these subjective ratings.

Another open-label trial of 20 multiple myeloma patients with chemotherapy-induced neuropathy reported that PEA treatment (300 mg twice daily) for 2 months significantly improved neurophysiological outcomes as measured by motor and sensory nerve fiber function and laser-evoked potentials [18]. The authors speculate that PEA moderates mast cell hyperactivity and relieves conduction blocks secondary to endoneural edema.

In a controlled trial in patients with carpal tunnel syndrome with entrapment neuropathy, PEA treatment (600 or 1200 mg/day) significantly improved carpal tunnel syndrome-induced reduction of median nerve latency time and this effect was dose-dependent [19]. This study did not have a placebo control. The full text was not accessible, and therefore details of this study could not be evaluated.

Several preclinical studies have also shown benefit of PEA in neuropathy. PEA treatment significantly increased thermal and mechanical thresholds in neuropathic mice (from spared nerve injury of the sciatic nerve) while improving cognitive functions [20]. PEA treatment prevented the increase in expression of a glutamate NMDA receptor subunit GluN2B protein and the synaptic protein PSD95 while increasing the neurotrophic factor BDNF in the prefrontal cortex. In rodent models of diabetic neuropathy, PEA decreased inflammation, relieved mechanical allodynia, counteracted nerve growth factor deficit, improved insulin levels, and preserved pancreatic cell morphology [21; 22].

Cardiovascular. UNKNOWN. In a biomarker study of 107 patients with impaired coronary function, higher circulating levels of PEA were associated with and predictive of worsened coronary function in morbidly obese individuals as well as in the overall cohort [23]. Circulating levels of PEA and VCAM1 were increased in morbidly obese individuals compared to normal weight subjects. Because endogenous PEA concentration can be elevated in other pathological conditions, the sensitivity and specificity of PEA need to be further investigated. Larger trials are needed to validate PEA as a potential circulating biomarker of coronary dysfunction in both morbidly obese patients and the general population.

In a double-blind randomized controlled trial of 40 patients with ocular hypertension, PEA (300 mg twice daily) for 3 months reduced intraocular pressure and led to significantly improved flow-mediated vasodilation compared to placebo [24]. This effect appeared to be due to improved peripheral endothelial function and its positive effect lasted longer than the duration of PEA intake.

In spontaneously hypertensive rats, PEA treatment (30 mg/kg/day) for 5 weeks significantly reduced blood pressure by downregulating the angiotensin receptor 1 and angiotensin-converting enzyme (ACE) [25].

Safety: Numerous clinical trials have shown that PEA is generally well-tolerated in people with chronic pain and other conditions, though a few adverse events including infection have been reported in some patient populations.

Types of evidence:

- 2 meta-analyses in people with pain
- 3 double-blind randomized controlled trials
- 1 single-blind clinical trial
- 2 open-label trials
- 1 observational study
- 1 case study
- 1 laboratory study testing safety of micronized PEA in culture and rodent models

Clinical data: Numerous clinical trials have tested the effects of PEA and none of the studies in patients with chronic pain have reported serious adverse events (SAEs) related to PEA, though a few studies in neuropathic pain and stroke patients reported SAEs that may or may not be related to PEA.

A 2017 meta-analysis included 10 randomized clinical trials with a total of 786 patients receiving PEA (and 512 controls) [11]. Doses used ranged from 300-1200 mg/day and trial durations ranged from 15-180 days. In the studies included, no adverse effects were reported in PEA-treated patients. However, adverse effects of low severity may not have been captured. Adverse events reported with PEA treatment in previous trials included gastrointestinal upset, drowsiness, and heart palpitations. All-cause dropout was lower in people receiving PEA (1.1%) compared to inactive controls (4.3%), though this difference was not statistically significant.

In a 2016 meta-analysis that included 12 clinical studies in people with chronic pain or neuropathic pain, micronized or ultramicronized PEA treatment (mostly 1200 mg/day, Normast®) for 30-365 days did not result in serious, non-serious, or suspected adverse events [13]. A total of 1,188 subjects received either micronized or unmicronized PEA.

In a double-blind randomized controlled trial of spinal cord injury-induced neuropathic pain, 7 out of 68 patients reported adverse effects, of which 5 were SAEs [16]. One patient who was treated with PEA committed suicide, which after careful investigation, was not considered to be related to the study drug. Other SAEs were urinary tract infection, paralytic ileus, cholecystolithiasis (gallstones), and erysipelas (bacterial skin infection) causing hospitalization in 3 patients treated with PEA and 1 treated with placebo. One patient treated with PEA had a fungus infection and 1 placebo treated patient experienced blurred vision.



In an open-label study of 250 stroke patients, 9 patients dropped out of the study: 2 due to death due to severity of disease, 3 due to transfer to another rehab center, 2 had onset of diarrhea, 1 had gastric discomfort, and 1 experienced agitation [1]. Tolerability of PEA for the remainder of the patients was excellent with no adverse events observed over the course of the study. Blood chemistry and hematology did not reveal any deviations from normal values.

In an open-label study of 30 diabetic patients with neuropathic pain, hematological and urine analyses did not reveal any alterations associated with micronized PEA treatment; no serious adverse events were reported [17].

In case studies of autistic boys, no adverse effects were noted with PEA for either of the patients [2].

Preclinical studies: In a safety/toxicity/genotoxicity study, PEA did not induce mutations in bacterial assays or in human cells [26]. In rats, PEA was found to have an LD₅₀ greater than the limit dose of 2000 mg/kg body weight. In a 90-day toxicity study, there were no differences in body, organ, or tissue weights and no gross abnormalities were found at necropsy other than incidental findings that were not dose-dependent.

Drug interactions: Drug interaction information was not available on Drugs.com and other sites. Based on its mechanism, PEA is likely to interact with other PPAR- α agonists such as clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate, which are used to treat high triglycerides.

Sources and dosing: PEA is produced in the body naturally. It is also found in soybeans, egg yolk, and peanut meal. PEA is available as a supplement in tablet, capsule, and powder forms. PEA is a poorly water-soluble substance and the dissolution rate is often the rate-limiting step for oral absorption and bioavailability [12]. Most clinical studies that have shown decreased chronic pain have used the Normast® brand of ultramicronized PEA at doses of 600 mg twice daily [13].

Research underway: There is currently one phase 3 study testing a combination of dronabinol and PEA in Tourette syndrome ([NCT03066193](#)). This study is scheduled to be completed in January 2019. A phase 4 study is testing the efficacy of ultra-micronized PEA in geriatric patients with chronic pain ([NCT02699281](#)). They were using an N-of-1 placebo-controlled randomized crossover design [27]. This study was scheduled to be completed in October 2016, though the status of this trial is unknown.

Search terms:

Pubmed, Google:

- + meta-analysis, + clinical trial, + cognitive, + ApoE4, + Alzheimer's, + blood-brain barrier, + cardiovascular, + diabetes, + neuropathy, + safety

Websites visited for palmitoylethanolamide, palmidrol:

- Clinicaltrials.gov (8 total, 2 ongoing)
- Examine.com (o)
- Treato.com (o)
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com (o)
- WebMD.com (o)
- [PubChem](#)
- DrugBank.ca (o)
- Labdoor.com (o)
- ConsumerLab.com (o)
- Pharmapro.com (ads)

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