Relief Elevator Pitch:

+PlusCBD-- Relief address minor aches and pains and low-grade chronic inflammation that drives all health issues.

Relief contains three of the most effective, non-habit-forming anti-inflammatories, CBDA/CBD and PEA offering a safe alternative to risky non-steroidal anti-inflammatories and dangerous opioid pain killers.

Relief is the first and only, triple action CBDA/CBD and PEA combination available.

Relief is an easy to swallow, soft gel capsule that targets all three pathways of pain and inflammation offering enhanced and synergistic effects for maximum comfort, and systemic relief.

+PlusCBD award winning products are the highest quality CBD products available and are backed by more science, than any other CBD available without prescription.

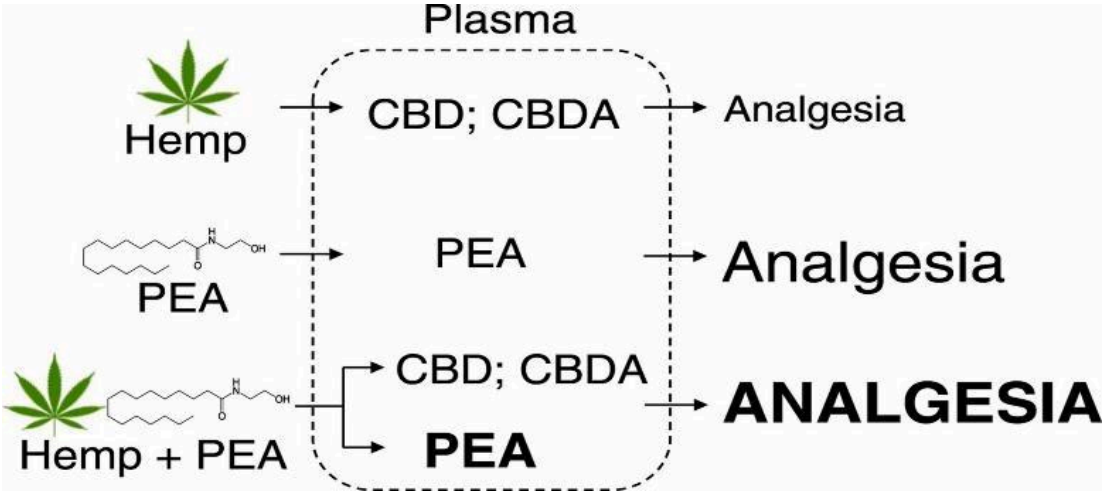
Experience the comfort and relief, you deserve.



How does Relief work? What makes it unique?

- Cannabis is extremely biologically active, and we have just begun unlocking the remarkable anti-inflammatory and immune supporting powers, of the plant. Relief works by restoring normal levels of your body's anti-inflammatory and analgesic agents and is more effective than using CBD, CBDA, or PEA alone. *

*. *Palmitoylethanolamide and hemp oil extract exert synergistic anti-nociceptive effects in mouse models of acute and chronic pain. Pharmacological Research* (2021)





3 pathways of pain summary

CBD-ECS is a key endogenous system regulating pain sensation with modulatory actions at all stages of pain processing. CBD also regulates innate immunity and inflammatory responses through the inhibition of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines.

CBDA- Selective COX-2 inhibitor modulate the first key steps in the synthesis of prostaglandins that convert AA into the hormone like compounds, that increase sensitivity to pain and thicken blood.

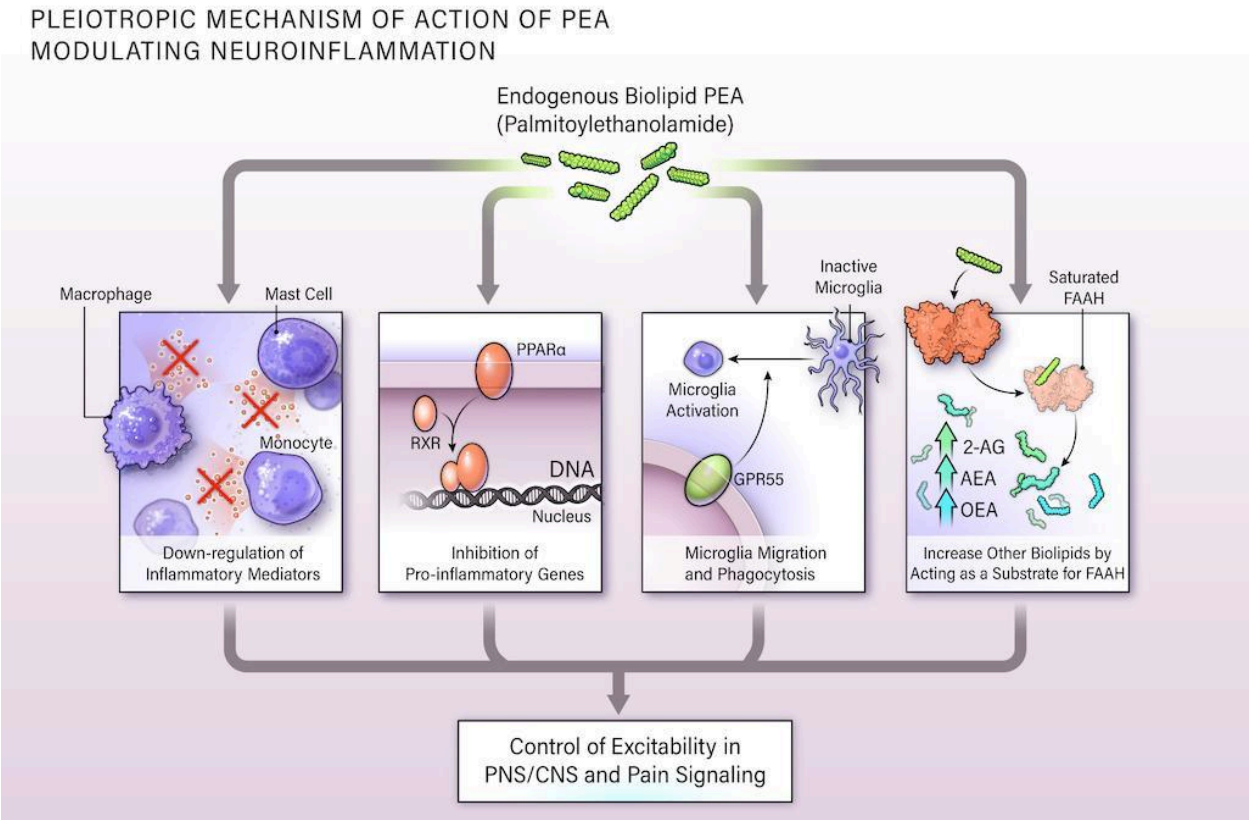
PEA- N-acylethanolamine acid amidase (NAAA) previously unrecognized control node in the transition from acute to chronic pain, which can be targeted by PEA.

What is PEA

Palmitoylethanolamide (PEA), is a non-habit forming endogenous bioactive lipid known to modulate neuroinflammation and pain signaling, representing a promising

potential mechanism to treat multiple conditions of chronic pain.

PEA is a broad modulator of inflammatory processes which also affect pain sensation and neuroprotection. Its mode of action has multiple effects (i.e., pleiotropic), as it involves many pathways and targets in both the peripheral and central nervous systems.



- Addresses large markets with growth opportunities in opioid-sparing indications (pain, post-surgical pain, morphine tolerance, etc.), endometriosis, osteoarthritis, fibromyalgia, etc.
- An endogenous compound, and a key regulator of endocannabinoid system in inflammation

- PEA increased expression of CB2 receptors
- PEA increases 2-AG and AEA, which directly activate CB1, CB2, and TRPV1 receptors
- PEA inhibits the activation of mast cells (peripheral)
- PEA reduces the activation of microglia and astrocytes (CNS)
- Clinical data available that suggests that FSD-PEA is superior to Ibuprofen and the opiates in the treatment of pain
- A well-researched compound in preclinical and clinical studies
- A “Pharmaceutically Green” API, a growing trend in inflammatory and related therapeutics

Sources of PEA

PEA was first identified in egg yolk and has been found in many food sources but getting enough PEA directly from the food is undoable, based on how much food you would need to eat. For example, you would need to eat 0.32 kg of soy lecithin, 42 kg of roasted coffee, or 2200kg–black-eyed peas to get the same levels of PEA as taking 175 mg of the patented PEA form known as Levagen+ PEA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7662788/pdf/ijms-21-07942.pdf

A double-blind randomised controlled study to evaluate the effectiveness of orally dosed Palmitoylethanolamide (PEA) compared to ibuprofen for reducing pain severity and duration of headaches in healthy participants aged 18 years and older.

Dr David Briskey, Amanda Rao

Methodology

Design

A double-blind randomised controlled study was undertaken to evaluate the effectiveness of orally-doses Palmitoylethanolamide (PEA) compared to ibuprofen for reducing pain severity and duration of headaches in healthy participants ages 18 years and older. Headache types were classified according to the *International Classification of Headache Disorders, 3rd edition* (ICHD3) published by the International Headache Society. All participants provided written informed consent and were screened as per the inclusion and exclusion criteria prior to commencing the study.

Participants

100 (50 per arm) healthy adult male or female participants, aged 18 years and older who had access to a computer or smartphone for questionnaire completion and had at least two headaches per month were recruited from databases and public media outlets to partake in the study. Participants were excluded based on the history or evidence of clinically significant disease,including, but not limited to, cardiovascular, neurological, psychiatric, renal, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Other exclusion criteria included the use of long-term medication (unless for controlled medical conditions as above), malignancy or treatment for malignancy within the previous 2 years, Chronic past and/or current alcohol use (>14 alcoholic drinks week), smokers and those allergic or hypersensitive to any of the ingredients in the PEA or ibuprofen formula. Females who were either pregnant, lactating or not taking a prescribed form of contraception (i.e. oral contraception pill, birth control implant e.g. implanon) were excluded from the study.

Intervention

Following recruitment, participants were allocated to one of the two treatment groups for the entire duration of the study using random allocation software. The study duration lasted for a maximum of 4 months, with participation concluding once 5 headache events were recorded. All subjects and investigators were blinded to the allocations during the entire study until all statistical analysis had been completed.

Study Preparations

The study arms were as follows: (1) Levagen+ Palmitoylethanolamide (PEA) (525mg) taken upon the onset of a headache and (2) ibuprofen (400mg), dosed as per the PEA arm. Both were to be taken orally with plain water. Investigational and comparator products were enclosed in trial product containers that were identical in function and appearance to ensure investigators and participants were blinded to the treatment arm until results were finalised.

Study Protocol

Following allocation to a treatment group, participants were asked to fill out a standardised questionnaire to assess their lifestyle, including questions about their: age, weight, height, level of physical activity, alcohol consumption, and work status. Upon the onset of headache symptoms, participants were asked to record the time and date of the occurrence and score the perceived headache pain using a Visual Analog Score (VAS) system in an electronic diary provided. They also recorded any gastrointestinal (GIT) intolerance. After this, they were to immediately supplement with a single dose (525 mg) of PEA or ibuprofen (400mg) with water. Participants then scored their headache pain (using VAS) and GIT tolerance every 30 minutes until the headache subsided, or until 4 hours had passed from headache onset (whichever occurs first) to provide pain and frequency data for analysis. If the headache pain did not subside within two hours, rescue medication (paracetamol) was permitted for use. Any rescue medication used was noted in the diary, while the headache pain continued to be scored. VAS scoring continued until either the pain subsided, or a further 2 hours had passed (4 hours from headache onset).

Participants were given enough product for 5 episodes of pain so that they could provide data for more than one pain event. During the trial, they were followed up every 4 weeks via phone calls until all 5 episodes had occurred or their involvement in the study came to an end (maximum 4 months). After study completion, a final health and lifestyle assessment, similar to the one at the start of the study, was conducted via questionnaire. Participants were monitored for any adverse effects that arose for the study duration.

Sample Size

Sample size was calculated using G*power (v3.0.10). Accounting for an α error probability of 0.05 and powered to 0.95 for a 25% reduction in VAS as a result of medication. The resulting effect size calculated from values obtained from published studies (baseline VAS of 45 and 48 mm for ibuprofen and treatment respectively), post intervention VAS score of 38 and 35 mm for ibuprofen and treatment respectively), was $d = 0.8$.

Statistical Analysis

Data were analysed with R (reference), using a range of native statistical functions and in some cases functions from the packages tidyverse, dplyr and ggplot. Slope analysis and some graphing was completed in Microsoft Excel.

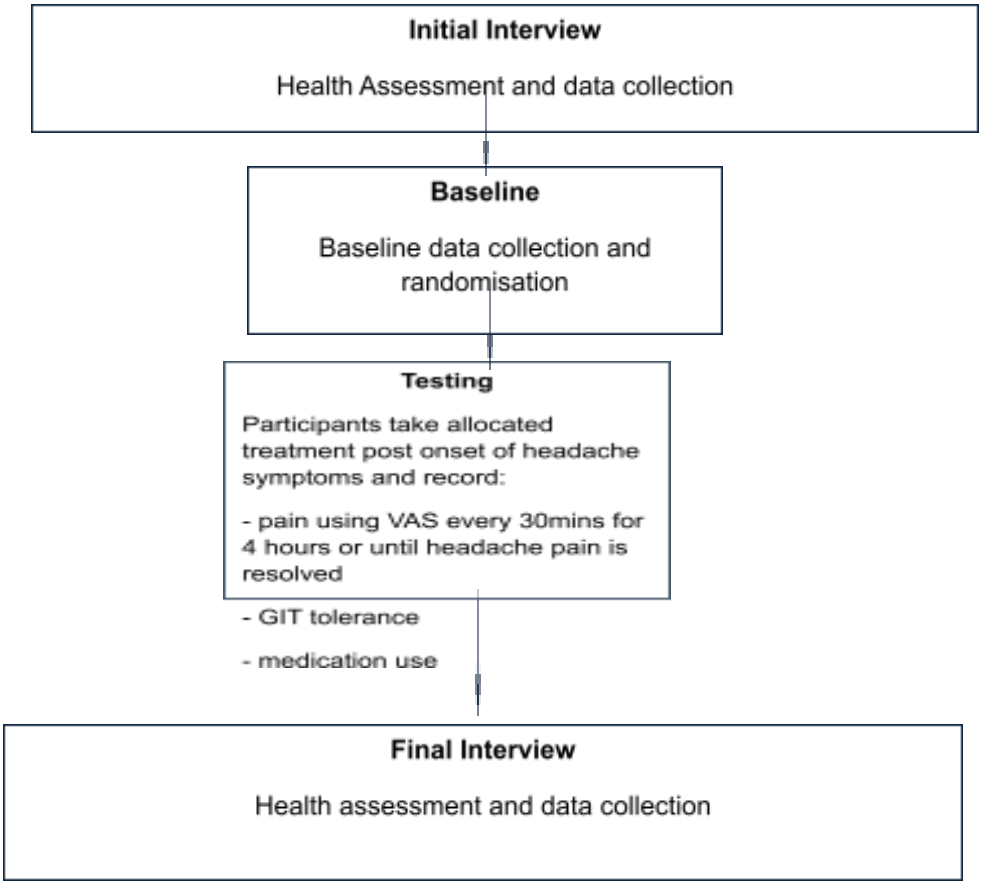
Following the International Headache Society (HIS) guidelines on treatment studies (Diener et al. 2019), the following metrics for treatment efficacy were selected for analysis:

- Proportion of events pain free at 2 hours (the Society's preferred primary clinical indicator)
- Proportion of significant reductions in pain at 2 and 4 hours: The guidelines recommend assessing change from severe or moderate to mild pain or none
- Mean change in pain score (calculated as pain reduction score) from baseline at 2 hours in the absence of rescue

- Proportion of events leading to rescue medication
- Proportion of events where the headache didn't resolve
- Of the headaches that resolved, the difference in time to resolution

The Guidelines point to the 2-hour threshold as an estimate of general patient and clinical expectations around headache relief.

Trial Design and Diagram
This is a randomised comparator controlled clinical trial.



Results

1. Baseline Characteristics

Eighty-six of the enrolled 100 participants reported at least one headache during the study period (42 in the Ibuprofen group and 44 in the Levagen+ group).

The number of headaches reported per participant were higher for Ibuprofen compared to Levagen+ (3.6 vs 2.7) with the total number of observations between products fairly similar (151 vs 120). These differences in sample size were not reported as unbalancing in any of the tests performed. (Table 1)

The majority of headaches were severe or moderate and mild headaches at onset were substantially the least common category. Severe headaches were the only category to differ between products in frequency.

Thresholds of VAS values of >65=severe, 30-65=moderate, and 1-29=mild were established for categorical analysis (as per HIS protocol) of reduction in pain following treatment.

Table 1. Starting condition values for headache study

	Ibuprofen 400mg	Levagen + 525mg
Mean VAS at time 0	59.64	56.68
# observations	149	120
# participants	42	44
Proportion of participants female	0.88	0.86
Proportion of observations female	0.87	0.87
Mean participant age (per observation)	42.58	39.63
# Mild at onset	14	12
# Moderate at onset	68	66
# Severe at onset	67	42

2. Proportion of events leading to rescue medication

The Cochran-Mantel-Haenszel Chi-Squared Test suggests that the difference in rescue frequencies between Ibuprofen and Levagen+ is significant (p~0.003)—overall, only 9% of participants took rescue medication while on Ibuprofen, but 23% took a rescue medication after taking Levagen+.

3. Proportion of events pain free at 2 hours and change in headache category

All data presented on pain relief is based on participants that did not take rescue medication.

Table 2 shows the proportion of participants pain free in each headache category.

Table 2. VAS means and proportion of participants pain free per product at two hours per headache category

	Ibuprofen	Levagen+
Proportion pain-free at 2 hours total	0.59*	0.43
Proportion pain free within 2 hours:		
moderate at onset	0.65*	0.42
severe at onset	0.49	0.45

Asterix codes: Statistically significant difference in means at 0.05>p>0.01*; 0.01>p>0.001**; p<0.001***

^Lack of significantly different result here is likely due to relatively small sample size of mild-at-onset data

Diener et al (2019) suggest that a categorial reduction in headache severity from severe or moderate to mild or none by two hours after treatment is a useful experimental endpoint. We analysed this endpoint at both two and four hours after treatment. Headaches that were mild at onset were by definition not included as measures of successful categorical reduction in severity. Where rescue medication was taken by the participant, these data were either excluded entirely or counted as a failure to reduce categorical severity in the event concerned (Table 3).

With rescues and mild-at-onset (i.e. VAS < 30) excluded from the analysis, the majority of headaches were resolved in both treatments by two hours, and almost all by four hours (Table 3).

Table 3. Categorical reductions in headache severity, rescues excluded

	Ibuprofen	Levagen+
No signif. reduction after two hours	23	23
No signif. reduction after four hours	3	8
Mild symptoms at onset	14	11
Proportion significantly reduced at two hours, no rescue ^	81.5%	72%

Proportion significantly reduced at four hours, no rescue^	97.6%	90%
Proportion not resolved within 2 hours, without rescues	0.36	0.44

^Proportion of headache events resulting in a significant reduction (measured categorically according to International Headache Society guidelines) excluding headaches that were mild at onset and any rescue events

†This proportion excludes mild-at-onset but includes rescue events **as failures to produce a reduction**

Asterix codes: Statistically significant difference in means at 0.05>p>0.01*; 0.01>p>0.001**; p<0.001***

4. **Mean change in pain score from baseline and proportional reduction in pain after 2 and 4 hours by headache category, rescues excluded**

Table 4. Reduction in pain score two and four hours after treatment in three severity categories for both products

	Ibuprofen	Levagen+
Mean proportional loss in VAS at two hours without rescues^	0.81	0.71
Mean PSR after two hours, mild headache	17.6	14.6
Mean PSR after two hours, moderate headache	43.6	37.0
Mean PSR after two hours, severe headache	58.1	50.3
Mean PSR after four hours, mild headache	19.3	16.9
Mean PSR after four hours, moderate headache	50.0	45.9
Mean PSR after four hours, severe headache	69.8	62.5
Proportional VAS reduction after two hours, mild headache	0.72	0.65
Proportional VAS reduction after two hours, moderate headache	0.86	0.73
Proportional VAS reduction after two hours, severe headache	0.77	0.68
Proportional VAS reduction after four hours, mild headache	0.78	0.75
Proportional VAS reduction after four hours, moderate headache	0.99	0.90

Proportional VAS reduction after four hours, severe headache	0.92	0.85

Although PSR sizes are consistently larger in Ibuprofen at both two and four hours after treatment, the differences were not significant at $p<0.05$ (Table 5).

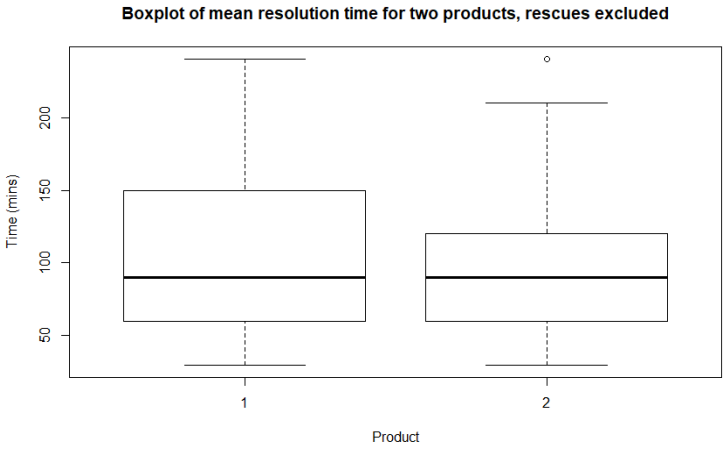
5. **Of the headaches that resolved, the difference in time to resolution**

With rescues excluded from resolved headache data, severe headache resolutions were significantly faster on average in Levagen+ than Ibuprofen. The reverse was true for mild headaches, but small sample sizes for mild headaches reduces the likelihood of finding a significant result. Moderate headache resolution times were effectively the same across products.

Table 5. Mean time to resolution (minutes) for two products, where a resolution was recorded

	Ibuprofen	Levagen+
Mean resolution time, rescues included	112.3	118.2
Mean resolution time, rescues excluded	106.3	101.0
Mean resolution time, mild	85.0	101.3
Mean resolution time, moderate	102.0	104.2
Mean resolution time, severe	116.9	95.5*

With rescue data included, mean resolution time (where resolutions were recorded) was similar between products, and just less than two hours on average:



Product 1 Ibuprofen, Product 2 Levagen+

6. **Regressions of pain scores assessed for the duration of the headache event, up to 4 hours, in the absence of rescue**

The modelling approach in general demonstrates that product is the most significant contributor (of the fixed effects) to differences in slope across the whole dataset. However, the differences were neither notably large nor highly statistically consistent. This part of the study supports the notion that the use of the two products resulted in broadly similar responses.

Gastrointestinal Tolerance

There were no serious adverse events reported in this study. Gastrointestinal tolerance was measured after each headache episode including nausea, abdominal pain, heartburn, diarrhoea or constipation. The incidence of gastrointestinal symptoms was similar in both groups (<15%), however as many of these symptoms (eg nausea) are commonly experienced with headaches it is difficult to attribute any of these symptoms directly to the products.

The New Triple Action Pain Relief Alternative

Occasional aches and pains are a common human experience, as we all feel the effects of physical over-exertion, minor injuries, increasingly sedentary lifestyles, and aging bodies. This causes many of us to reach for traditional pain medications almost daily. However, awareness of the negative impact that long term use of OTC pain killers has on our bodies is increasing, leading pain sufferers to search elsewhere for safe and effective alternatives.

New on the shelves is +PlusCBD Relief for anyone experiencing the minor aches and pains and low-grade chronic inflammation that seems to drive all health issues. +PlusCBD Relief offers the first and only triple action combination of CBD, CBDA, and PEA (palmitoylethanolamide) available to consumers. This powerful trio is more effective when used together in the Relief formula than just taking CBD, CBDA, or PEA alone. Let's take a look at these three powerful ingredients and how they contribute to greater soreness support.

Cannabidiol (CBD)

The major cannabinoid found in hemp, CBD interacts with the body's endocannabinoid system to support physical, mental, and emotional balance, helping maintain a healthy inflammatory response and regulating pain sensation with modulatory actions at all stages of pain processing by the body. CBD also plays a role in regulating innate immunity and inflammatory responses through the inhibition of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines. +PlusCBD Relief uses CO2 extracted full spectrum hemp that has been distilled for maximum strength potency. +PlusCBD is backed by more science than any other CBD brand available without a prescription.

Cannabidiolic Acid (CBDA)

CBDA is the acid bound form of CBD, and unlike commonly used ethanol or butane extraction, the patented water-based extraction method used by +PlusCBD for its CBDA does not use heat or harsh chemicals to produce the purest source of CBDA. This water extracted CBDA is known to have increased bioavailability and offers its own set of unique physiological benefits. CBDA helps support a healthy inflammatory response by selectively modulating the COX2 enzyme pathway and helps promote a healthy gut.

Levagen® + (PEA)

PEA, or palmitoylethanolamide, is an endocannabinoid like compound made by the human body. Relief softgels feature patented Levagen®+ PEA, which has been shown in human clinical studies to support a healthy immune, inflammatory, neurological, and nerve function response.

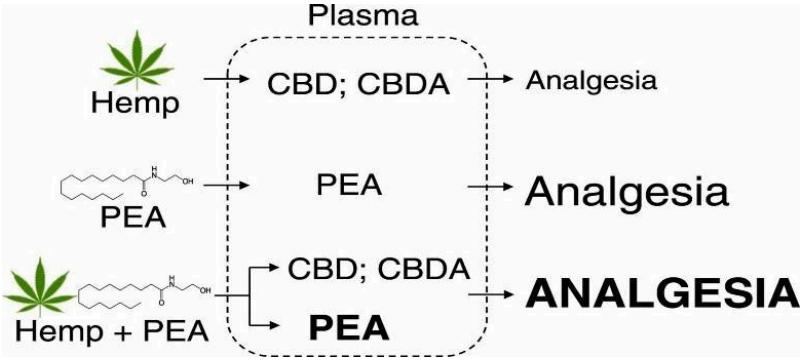
High stress lifestyles and poor nutrition can lead to a deficiency of PEA. As a daily supplement, Levagen®+ PEA provides many of the same benefits as CBD and has been shown clinically to be more effective at reducing pain than common non-steroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen. PEA is a broad modulator of the inflammatory processes that affect pain sensation and neuroprotection. Its mode of action has multiple effects (i.e., pleiotropic), as it involves many pathways and targets in both the peripheral and central nervous systems.

2,500 patients have been treated with PEA for various pain conditions in more than 30 clinical studies. Fifteen of these studies were randomized, controlled trials (RCTs) with a total of approximately 1,500 patients where PEA consistently demonstrated statistically significant reductions in pain with favorable safety and tolerability. The largest study published so far was a multicenter, double-blind randomized study on three groups (placebo, 300, and 600 mg PEA) of 636 total patients with a treatment duration of 3 weeks. These patients suffered low back pain/sciatica, and PEA was found to be efficacious and extremely well tolerated.

The authors reported a Number Needed to Treat (NNT) for ≥50% pain relief was much lower than the treatments commonly used. Number to Treat (NNT) is specific to an outcome, which in this case is ≥50% Pain relief in lumbosciatic algias with only 1.7 people needing to take 600 mg of PEA (343 mg Levagen®+ PEA) daily for 1 person to experience ≥50% pain relief from low back pain due to compression of the sciatic nerve. PEA has no overt toxicity, even at high doses, and clinical trials have reported that the compound is very well tolerated, making it ideal for daily use.

Relief softgels are more effective than using CBD, CBDA, or PEA alone.

+PlusCBD Relief is powered by three of the most effective, non-habit-forming anti-inflammatories available -- CBDA, CBD, and PEA -- offering a safe alternative to risky non-steroidal anti-inflammatories and dangerous opioid pain killers. +PlusCBD Relief softgels support normal levels of your body's natural anti-inflammatory and analgesic agents for maximum comfort and systemic relief.



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Micronized Palmitoylethanolamide: A Post Hoc Analysis of a Controlled Study in Patients with Low Back Pain – Sciatica

CNS & Neurological Disorders - Drug Targets, 2019, 18, 491-495

NNT is specific to an outcome, which in this case is "≥50% Pain relief in lumbosciatic algias".

Results: Compared with placebo, palmitoylethanolamide 600 mg/die yielded a number needed to treat of 1.7 (95% confidence interval: 1.4-2) for pain, and 1.5 (95% confidence interval: 1.4-1.7) for function. The correlation between the five categories was highly significant for pain relief though not significant for reduced dysfunction.

Conclusion: Palmitoylethanolamide was extremely effective on pain and function in a large cohort of patients with low back pain – sciatica. Although, the multiple mechanisms of action of palmitoylethanolamide are ideal for mixed pain conditions such as low back pain – sciatica, the correlation between pain relief and the likelihood of neuropathic pain suggests that this drug exerts a predominant action on the neuropathic pain component.

So, 1.7 people would need to take 600 mg of micronized PEA daily for 1 person to experience ≥50% pain relief from low back pain due to compression of the sciatic nerve.

Study	Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study	A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis
Population	Armenian adults w/ degenerative hypertrophic OA of the knee (93% female?!)	Adults with mild to moderate knee osteoarthritis
Sample size	n=201 (179 completed)	n=120 (111 completed)
Intervention	1. Curamin (350 mg BCM-95® and 150 mg Boswellia serrata) 2. CuraMed (552–578 mg of BCM-95) 3. Placebo One capsule (500 mg) orally, three times daily.	1. 300 mg PEA 2. 600 mg PEA 3. Placebo Oral. Daily in divided doses.
Duration	12 weeks (3 study visits)	8 weeks (? Study visits)
Design:	Randomized, double-blind, placebo-controlled, three-arm parallel-group, trial	Randomized, double-blind placebo-controlled study
Outcome measures:	**Primary**: 1. OA physical function performance-based tests 2. WOMAC 3. Self-reported global assessment of disease severity **Secondary**: 1. Blood samples 2. Adverse effects	**Primary**: 1. WOMAC **Secondary**: 1. Numerical Rating Scales (NRS) for pain 2. Depression Anxiety Stress Scale (DASS) 3. Perceived Stress Scale (PSS) 4. Pittsburg Sleep Quality Index (PSQI) 5. Short Form Health Survey (SF-36)
Comments:	**Total WOMAC score**: ● Average score at baseline around 30 (out of 100). Mild to moderate pain, stiffness and physical function. ● Lower average score than the Levagen study. ● Curamin: **Approximate 22% reduction in total WOMAC score over 12 weeks.** Statistically significant. ● Curamed: **Approximate 22% reduction in total WOMAC score over 12 weeks.** Statistically significant. ● Difference between Curamin and placebo is statistically significant. Difference between Curamed and placebo is not. **WOMAC pain subscale:**	**Total WOMAC score**: ● Average score at baseline around 40 (out of 100). Moderate pain, stiffness and physical function. ● Dose-response relationship seen. Levagen 600 led to a greater reduction in total WOMAC score than Levagen 300, but this difference does not appear to be statistically significant different. ● **Approximately 50% reduction in average total WOMAC score for Levagen 600 over 8 weeks.** ● Difference between Levagen 600 and placebo appears to be statistically significant (Can't tell for sure w/o the paper).

	● Average score at baseline around 6 (out of 20). Mild to moderate pain. **Lower average score than the Levagen study.** ● Curamin: **Approximately 32% reduction in average WOMAC pain score for Curamin over 12 weeks.** Statistically significant. ● Curamed: **Approximately 31% reduction in average WOMAC pain score over 12 weeks.** Statistically significant. ● Curamin: **Approximately 31% reduction in average WOMAC pain score over 12 weeks.** Statistically significant.	**WOMAC pain subscale**: ● Average score at baseline around 9 (out of 20). Moderate pain. ● Dose-response relationship seen. Levagen 600 led to a greater reduction in pain score than Levagen 300, but this difference does not appear to be statistically significant different. ● Difference between Levagen 600 and placebo appears to be statistically significant. Difference between Levagen 300 and placebo is almost significant. ● **Approximately 55% reduction in average WOMAC pain score for Levagen 600 over 8 weeks.**
	WOMAC stiffness and function: ● Not analyzed	**WOMAC stiffness and function**: ● Similar trends observed
	● Overall, it appears that Levagen 600 mg is more effective at reducing OA pain, stiffness, and dysfunction than Curamin or Curamed. ● Curamin – lower dose of curcuminoids, plus Boswellia – appears to be more effective than Curamed. ● The average total WOMAC score at baseline was approximately 30% greater in the Levagen study, so these individuals had more pain and dysfunction. And, experienced a greater reduction than those in the Curamin/Curamed study. ● **Caveat:** I haven't actually read the Levagen study! ● I think you could use this comparison to make the argument that Levagen outperforms Curamin. And, that Curamed is not better than placebo.	