

# **Palmitoylethanolamide (PEA) in Age-Related and Neurodegenerative Brain Conditions: A Comprehensive Review of Historical Development, Mechanistic Insights, and Therapeutic Promise**

## **Section 1: The Scientific Trajectory of an Endogenous Mediator: A Historical Perspective**

The journey of Palmitoylethanolamide (PEA) from a little-known lipid in food to a promising therapeutic agent for complex neurological diseases is a compelling narrative in modern pharmacology. Its history is characterized by periods of intense interest interspersed with decades of scientific neglect, a trajectory shaped almost entirely by the evolving understanding of its biological mechanism. This section traces the path of PEA, highlighting the key discoveries and conceptual breakthroughs that have defined its development.

### **1.1 The Serendipitous Discovery (1940s-1950s)**

The story of PEA does not begin with targeted drug design but with astute clinical observation. In the early 1940s, physicians working with underprivileged children made a curious finding: supplementing their diets with dried chicken egg yolk appeared to reduce the recurrence of rheumatic fever, even in the presence of ongoing streptococcal infections.<sup>1</sup> This observation sparked scientific inquiry into the components of common foodstuffs.

Throughout the 1950s, researchers demonstrated that purified lipid fractions from egg yolk, as well as from peanut oil and soy lecithin, possessed distinct anti-allergic and anti-inflammatory properties in animal models.<sup>1</sup> The search for the specific active

agent culminated in 1957, when a team of scientists led by F.A. Kuehl Jr. at the pharmaceutical company Merck & Co. successfully isolated and identified the compound responsible for these effects. They named it N-(2-hydroxyethyl)-palmitamide, now universally known as Palmitoylethanolamide, or PEA.<sup>3</sup> Initial isolations were made from sources including soy lecithin, egg yolk, and peanut flour.<sup>7</sup>

## 1.2 A Period of Clinical Use and Scientific Stasis (1960s-1980s)

The discovery of PEA was followed by a crucial finding in 1965: its identification in mammalian tissues, which confirmed that PEA was not merely a dietary component but an endogenous molecule produced within the body.<sup>3</sup> This validation spurred a phase of clinical investigation.

The most significant clinical exploration of PEA during this era occurred in the former Czechoslovakia. Marketed under the trade name Impulsin by the pharmaceutical firm SPOFA, PEA was administered in tablet form to thousands of individuals, including children and soldiers, during the 1970s. A series of clinical trials demonstrated its efficacy and safety in reducing the severity and duration of symptoms associated with influenza and other acute respiratory infections.<sup>1</sup> A similar product, Palmidrol, was introduced in Spain for the same indications.<sup>11</sup>

Despite this documented clinical success and apparent safety, PEA failed to capture sustained interest from the broader international scientific and medical communities. Research gradually slowed, and PEA eventually faded from clinical use. This "period of research stasis," which lasted for more than two decades, was not due to findings of toxicity or lack of efficacy.<sup>1</sup> Instead, it was a direct consequence of a critical knowledge gap: the failure to identify a specific molecular target or a plausible mechanism of action. Without a clear understanding of

how PEA worked, it remained a pharmacological curiosity, unable to be integrated into the receptor-based paradigms that dominated drug development.

## 1.3 The Montalcini Renaissance (1990s)

The "resurrection" of PEA as a subject of serious scientific inquiry can be attributed to the work of one of the 20th century's most eminent neurobiologists, Nobel laureate Professor Rita Levi-Montalcini.<sup>12</sup> In a landmark 1993 paper, her research group provided the missing piece of the puzzle, fundamentally reframing the understanding of PEA's biological role.<sup>12</sup>

Levi-Montalcini and her colleagues demonstrated that PEA functions as a natural modulator of hyperactive mast cells, key players in the inflammatory response.<sup>12</sup> They proposed that PEA is an "autacoid local injury antagonist" (ALIA)—an endogenous substance synthesized "on-demand" in response to injury or inflammation to restore local tissue homeostasis.<sup>1</sup> To describe this new class of regulatory molecules, she coined the term "ALIAmide".<sup>9</sup> This elegant concept provided the first compelling biological mechanism for PEA's long-observed anti-inflammatory effects. It positioned PEA not as an external drug, but as a key component of the body's own self-regulating and protective systems.

This discovery was transformative. By linking PEA to the regulation of non-neuronal cells like mast cells, which form a critical bridge in the neuro-immune axis, Levi-Montalcini's work provided the scientific rationale that had been missing for decades.<sup>11</sup> Occurring alongside the discovery and exploration of the endocannabinoid system—a signaling network to which PEA is biochemically and functionally related—the ALIAmide concept reignited global scientific interest, paving the way for the modern era of PEA research.<sup>1</sup>

The historical arc of PEA serves as a powerful case study on the primacy of mechanistic understanding in therapeutic development. The positive clinical data from the Impulsin trials of the 1970s, while significant, were ultimately insufficient to sustain scientific and pharmaceutical momentum because they were purely phenomenological—they described *what* happened, but not *why*. The two-decade stasis that followed demonstrates that without a plausible biological rationale, even a safe and effective compound can be relegated to obscurity. It was only when Levi-Montalcini provided a compelling mechanistic framework—the ALIA concept—that PEA could be re-evaluated as a legitimate therapeutic candidate. This history explains why research is accelerating now, more than half a century after its initial discovery, and underscores a fundamental principle: in the progression from observation to medicine, demonstrating *how* a molecule works is as critical as demonstrating *that* it works.

## 1.4 Historical Milestones in PEA Research

The following table summarizes the key events that have shaped the scientific understanding and therapeutic application of Palmitoylethanolamide.

Decade	Key Event/Discovery	Key Researchers/Groups	Significance	Source IDs
1940s	Clinical observation that dried egg yolk in diets reduced rheumatic fever recurrence.	Clinicians (e.g., Coburn)	The first hint of a potent anti-inflammatory agent in a common food source, sparking initial scientific inquiry.	<sup>1</sup>
1950s	Isolation and identification of Palmitoylethanol amide (PEA) as the active anti-inflammatory agent from egg yolk.	F.A. Kuehl Jr. (Merck & Co.)	The formal discovery and chemical characterization of the molecule, giving researchers a specific compound to study.	<sup>3</sup>
1960s	Identification of PEA in mammalian tissues.	Bachur et al.	Confirmed that PEA is an endogenous molecule, not just a dietary substance, suggesting it has a natural physiological role.	<sup>3</sup>
1970s	Clinical use of PEA (Impulsin®) in Czechoslovakia for influenza	SPOFA (pharmaceutical company)	Large-scale human data demonstrated the safety and efficacy of PEA,	<sup>1</sup>

	and respiratory infections in thousands of patients.		though the mechanism remained unknown.	
<b>1980s</b>	"Period of Research Stasis." PEA is withdrawn from the market and scientific interest wanes.	N/A	A critical period of neglect driven by the failure to identify a molecular target, highlighting the importance of mechanistic understanding in drug development.	<sup>1</sup>
<b>1990s</b>	"The Montalcini Renaissance." PEA is identified as a natural modulator of mast cells. The "ALIAmide" concept is born.	Prof. Rita Levi-Montalcini's group	Provided the first plausible biological mechanism for PEA's action, reigniting global research interest and linking PEA to the neuro-immune system.	<sup>9</sup>
<b>2000s-Present</b>	Elucidation of molecular targets (PPAR- $\alpha$ ), development of advanced formulations (um-PEA, PEA-LUT), and advanced clinical trials.	Various international research groups	The modern era of PEA research, characterized by a deep understanding of its pharmacology, the technological ability to enhance its bioavailability, and high-quality clinical trials in neurodegenerati	<sup>7</sup>

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## Section 2: The Pleiotropic Pharmacology of PEA: Mechanisms of Neuroprotection

Palmitoylethanolamide is not a conventional drug that targets a single receptor or enzyme. It is a pleiotropic lipid mediator, meaning it acts on multiple molecular targets to orchestrate a complex, coordinated response. Its primary function is to serve as an endogenous homeostatic regulator, mobilized by the body to resolve inflammation and protect cells from damage. Understanding this multi-target pharmacology is essential to appreciating its potential in treating multifaceted conditions like neurodegenerative diseases, where inflammation, oxidative stress, and neuronal dysfunction are deeply intertwined.

### 2.1 A Homeostatic Regulator, Not a Simple Drug

The foundational concept for understanding PEA's action is the one proposed by Levi-Montalcini: it is an "autacoid local injury antagonist" (ALIA).<sup>1</sup> This means that PEA synthesis is naturally upregulated in tissues that are under stress or have been injured.<sup>16</sup> This response is an intrinsic protective mechanism designed to restore local homeostasis. For instance, PEA levels have been found to increase in the brain in conditions such as Alzheimer's disease, Parkinson's disease, and traumatic brain injury, supporting the idea that it is part of the body's endogenous attempt to counteract the pathological process.<sup>16</sup> This mode of action—enhancing the body's own resolution pathways—is fundamentally different from that of most pharmaceutical drugs, which typically impose a powerful blockade or activation on a specific pathway.

### 2.2 Key Molecular Targets and Pathways

PEA achieves its effects through a sophisticated interplay of direct and indirect actions on several key signaling systems.

- **Peroxisome Proliferator-Activated Receptor-alpha (PPAR- $\alpha$ ) Activation:** A primary and well-established mechanism of action is the direct binding to and activation of PPAR- $\alpha$ , a nuclear receptor that plays a critical role in regulating gene expression related to lipid metabolism and inflammation.<sup>17</sup> Activation of PPAR- $\alpha$  by PEA leads to a downstream cascade that suppresses the production of pro-inflammatory proteins and enhances cellular protection. The importance of this pathway has been unequivocally demonstrated in animal models of Alzheimer's disease, where the neuroprotective effects of PEA were absent in mice genetically engineered to lack the PPAR- $\alpha$  receptor, confirming it as an essential target for PEA's therapeutic action.<sup>22</sup>
- **The "Entourage Effect" and the Endocannabinoid System:** PEA is structurally related to the endocannabinoid anandamide (AEA) and is often classified as a cannabimimetic compound or an N-acylethanolamine (NAE).<sup>9</sup> However, it is not a classical cannabinoid, as it possesses very weak to no affinity for the primary cannabinoid receptors, CB1 and CB2.<sup>1</sup> Instead, PEA exerts a powerful indirect influence on the endocannabinoid system through a mechanism known as the "entourage effect." It achieves this by inhibiting the activity of Fatty Acid Amide Hydrolase (FAAH), the primary enzyme responsible for breaking down anandamide.<sup>6</sup> By slowing the degradation of AEA, PEA effectively increases the levels and prolongs the action of this key endocannabinoid at CB1 and CB2 receptors, thereby contributing to the system's overall anti-inflammatory and analgesic tone without directly binding to the receptors itself.<sup>2</sup>
- **Other Receptor Interactions:** The pharmacology of PEA extends beyond these two core pathways. Research has shown that it can also directly activate two orphan G-protein coupled receptors, GPR55 and GPR119, whose functions are still being fully elucidated but are implicated in metabolic and inflammatory signaling.<sup>1</sup> Furthermore, PEA may act as a positive allosteric modulator of the Transient Receptor Potential Vanilloid type-1 (TRPV1) channel, a key receptor involved in pain signaling.<sup>5</sup> This multi-target engagement allows PEA to exert a broad spectrum of beneficial effects across different cell types and pathological processes.

## 2.3 Taming Neuroinflammation: Modulating Non-Neuronal Cells

A unifying feature of nearly all age-related and neurodegenerative brain conditions is chronic, low-grade neuroinflammation.<sup>23</sup> This sustained inflammatory response, primarily driven by non-neuronal glial cells, is no longer considered a mere consequence of neuronal death but is now understood to be a crucial driver of the neurodegenerative process itself.<sup>9</sup> PEA's main neuroprotective strategy is to quell this damaging inflammation by modulating the activity of these key cellular players.

- **Microglia and Astrocytes:** These are the resident immune cells of the central nervous system. In a pathological state, they become activated and release a barrage of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha, or TNF- $\alpha$ ; interleukin-1-beta, or IL-1 $\beta$ ) and reactive oxygen species that are toxic to surrounding neurons.<sup>26</sup> PEA, primarily through its activation of PPAR- $\alpha$ , has been shown repeatedly in preclinical models to down-modulate this glial activation. It shifts these cells away from a pro-inflammatory state and towards a more protective, homeostatic phenotype, thereby reducing neuronal damage. This mechanism is central to its observed benefits in models of Alzheimer's disease, Parkinson's disease, and stroke.<sup>21</sup>
- **Mast Cells:** As first identified by Levi-Montalcini, mast cells are another critical target. These immune cells reside in the brain and its surrounding tissues and can degranulate to release potent inflammatory mediators. PEA effectively inhibits this activation and degranulation, severing a key link in the inflammatory cascade.<sup>11</sup>

## 2.4 The Formulation Imperative: Unlocking PEA's Potential

The biological discovery of PEA's mechanisms is only half of the story of its modern success. The molecule itself presents a significant pharmaceutical challenge: as a long-chain fatty acid amide, PEA is highly lipophilic (fat-soluble), which makes it practically insoluble in water and, consequently, very poorly absorbed and bioavailable when administered orally in its naive, crystalline form.<sup>18</sup> This limitation historically hindered its therapeutic development. The remarkable clinical results reported in recent years are almost entirely attributable to the application of advanced pharmaceutical technology designed to overcome this hurdle.

The clinical emergence of PEA is therefore a story of synergy between biological discovery and technological innovation. The positive outcomes seen in modern trials are not simply a property of the PEA molecule itself, but of the *formulated* PEA product. This recognition that the method of delivery is as crucial as the active

ingredient is fundamental to understanding its current therapeutic status and future potential. It explains why a molecule discovered in the 1950s is only now gaining significant clinical traction, as the technology required to make it effective has matured. When evaluating evidence, it is therefore inaccurate to speak of "PEA" in general terms; one must specify the formulation, as results from naive PEA are not comparable to those from its bio-enhanced forms.

- **Micronization and Ultramicronization (m-PEA/um-PEA):** The most significant technological advance has been the development of micronized and ultramicronized PEA. Using a process called jet milling, the particle size of the raw PEA material is dramatically reduced from hundreds of microns to a range of less than 10 microns.<sup>18</sup> This process does not change the molecule's chemical structure but vastly increases its collective surface area, which facilitates better dissolution and absorption in the gastrointestinal tract. Studies have confirmed that ultramicronized PEA (um-PEA) demonstrates superior oral efficacy and absorbability compared to naive PEA, enabling it to achieve therapeutically relevant concentrations in target tissues, including the brain and spinal cord.<sup>7</sup>
- **Co-ultramicronization with Luteolin (PEA-LUT):** A further refinement is the combination of PEA with other beneficial compounds. While PEA is a powerful anti-inflammatory agent, it lacks significant direct antioxidant effects.<sup>29</sup> Neurodegenerative diseases are driven by both inflammation and oxidative stress. Luteolin is a natural flavonoid, found in many fruits and vegetables, with potent antioxidant and anti-inflammatory properties.<sup>33</sup> By co-ultramicronizing PEA with luteolin, a synergistic formulation (often denoted as PEA-LUT or co-ultraPEALut) is created. This combination product is designed to simultaneously and more effectively target both of the core pathological pillars of neurodegeneration. Many of the most impressive clinical results, particularly in Frontotemporal Dementia and Mild Cognitive Impairment, have been achieved with this specific synergistic formulation.<sup>15</sup>

### **Section 3: A Review of Evidence in Neurodegenerative and Age-Related Conditions**

The renewed interest in Palmitoylethanolamide, fueled by mechanistic insights and advanced formulations, has led to a growing body of research exploring its efficacy across a range of challenging neurological disorders. The evidence, however, is not

uniform. It exists on a spectrum, from high-quality, randomized controlled trials in some conditions to compelling but preliminary case reports and preclinical data in others. A sophisticated understanding requires a nuanced, condition-by-condition analysis of the data, acknowledging both the strength and limitations of the current evidence base.

### **3.0 Summary of Evidence for PEA in Neurodegenerative and Age-Related Brain Conditions**

The following table provides a comprehensive overview of the clinical and preclinical evidence for PEA across the key conditions discussed in this report. It is designed to serve as a high-level summary, collating the most critical data points regarding study design, intervention, and outcomes, thereby highlighting the varying strength of evidence for each application.

Condition	Study Type	Population	PEA Formulation & Dosage	Remarkable Outcomes (with quantitative data)	Limitations/Context	Source IDs
<b>Frontotemporal Dementia (FTD)</b>	Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial	48 patients with probable FTD	Co-ultramericized PEA-LUT (700 mg + 70 mg) twice daily for 24 weeks	<b>Slowing of Disease Progression:</b> Mean change on CDR-FTD-SoB scale was 0.53 for PEA-LUT vs. 1.39 for placebo ( $p=0.005$ ). <b>Less Functional Decline:</b> Significant	Highest quality evidence available for PEA in any neurodegenerative disease. Suggests a disease-modifying effect.	15

				ly better scores on ADCS-ADL.		
<b>Post-Stroke Recovery</b>	Open-label clinical study; other clinical trials	250 stroke patients in neurorehabilitation	Co-ultramicrodized PEA (700 mg) + luteolin (70 mg) daily for 60 days	<p><b>Cognitive Improvement:</b> Average MMSE score increased from 20.2 to 22.7 in 30 days.</p> <p><b>Functional Gains:</b> Significant improvements in neurologic al status, spasticity, pain, and daily living activities.</p>	Compelling results, but the largest study was open-label, which is a significant limitation as stroke patients show spontaneous recovery.	22
<b>Parkinson's Disease (PD)</b>	Observational adjuvant treatment study; case reports	PD patients on existing levodopa therapy	Ultramicrodized PEA (um-PEA) 1200 mg/day, reducing to 600 mg/day, for 1 year	<p><b>Reversal of Disease Severity:</b> Hoehn &amp; Yahr (HY) scale score progressed from 1.8 to 2.5 pre-trial; after 1 year of um-PEA, score improved to 1.9.</p> <p><b>Symptom Improvement:</b></p>	Data is not from an RCT. The HY scale result is extraordinary but requires rigorous confirmation.	17

				<b>ent:</b> Significant gains in motor, non-motor (mood, fatigue, sleep), and daily living activities.		
<b>Amyotrophic Lateral Sclerosis (ALS)</b>	Case reports; a "larger study"	Sporadic and familial ALS patients	Ultramicro nized PEA (um-PEA)	<b>Delayed Progression:</b> Slower decline in respiratory function; delayed need for tracheotomy and death. <b>Functional Improvement:</b> Improved muscle force and respiratory efficacy.	In a fatal disease, delaying hard endpoints like tracheotomy is profoundly significant. Evidence is not from an RCT.	28
<b>Mild Cognitive Impairment (MCI)</b>	Single case study	Elderly female with amnestic-MCI	PEA-LUT therapy for 9 months	<b>Cognitive &amp; Biomarker Normalization:</b> Neuropsychological evaluation became "almost normal." SPECT imaging	An exceptionally powerful result, but from a single patient. The objective biomarker data strongly corroborate this finding.	9

				showed "normalized hypometabolism."	es the clinical finding.	
<b>Alzheimer's Disease (AD)</b>	Numerous <i>in vitro</i> and <i>in vivo</i> preclinical studies	Animal models of AD (e.g., 3xTg-AD mice)	PEA, um-PEA, PEA-LUT	<b>Preclinical Efficacy:</b> Rescued cognitive deficits, reduced A $\beta$ formation and tau hyperphosphorylation, prevented A $\beta$ -induced cell death, and restrained neuroinflammation and oxidative stress.	Very strong and consistent preclinical rationale. However, there is a complete absence of human clinical trial data in the available research.	30

This hierarchy of evidence—from a Phase 2 RCT at the top to strong preclinical data at the base—directly informs the level of clinical confidence and dictates the logical next steps for research. For FTD, the evidence supports advancing to larger, pivotal trials. For conditions like PD and MCI, the remarkable but less rigorously obtained results create an urgent need for confirmation through well-designed RCTs. For AD, the robust preclinical foundation provides a compelling rationale to now initiate the first human pilot studies.

### 3.1 Frontotemporal Dementia (FTD): The Strongest Clinical Evidence

Frontotemporal dementia is a devastating neurodegenerative disorder that primarily affects individuals in their prime, leading to profound changes in behavior, personality,

and language. It is one of the leading causes of presenile dementia, and crucially, there are currently no approved disease-modifying treatments.<sup>15</sup> It is in this challenging context that PEA has produced its most robust and compelling clinical evidence to date.

A landmark Phase 2, monocentric, randomized, double-blind, placebo-controlled trial published in 2025 investigated the effects of co-ultramicronized PEA combined with luteoline (PEA-LUT) in FTD patients.<sup>15</sup> The study enrolled 48 patients with a diagnosis of probable FTD, who were randomly assigned to receive either PEA-LUT (700 mg PEA + 70 mg luteolin, twice daily) or a matching placebo for 24 weeks. The primary efficacy outcome was the change in a comprehensive disease severity scale, the CDR plus NACC FTLD—Sum of Boxes (SoB), which measures global, functional, and behavioral aspects of the disease.<sup>15</sup>

The results were remarkable. Patients in the placebo group showed the expected progressive decline over the 24-week period, with their mean CDR-FTD-SoB score worsening by 1.39 points. In stark contrast, the group receiving PEA-LUT showed significantly less decline, with their score worsening by only 0.53 points. The estimated mean difference between the groups was 0.86, a statistically and clinically significant result ( $p=0.005$ ) that indicates the treatment cut the rate of global disease progression by more than half.<sup>15</sup>

This benefit was supported by key secondary outcomes. Patients treated with PEA-LUT experienced significantly less functional decline in their ability to perform activities of daily living, as measured by the ADCS-ADL scale. They also showed a significant advantage in preserving language function, evaluated by the SAND scale.<sup>15</sup> An earlier, shorter-duration study had also reported that PEA-LUT improved frontal lobe function and reduced behavioral disturbances in FTD patients.<sup>28</sup> The Phase 2 trial was well-tolerated, with no significant differences in adverse events between the treatment and placebo groups. These findings represent the highest quality of evidence available for PEA in any neurodegenerative disease and provide a strong rationale for its potential as the first disease-modifying therapy for FTD.

### **3.2 Post-Stroke Recovery: Evidence of Functional and Cognitive Restoration**

Stroke remains a leading cause of long-term disability, and therapies that can enhance recovery are of critical importance. Several studies suggest that PEA,

particularly in combination with luteolin, can significantly improve outcomes for stroke survivors.

The largest study was an open-label clinical trial involving 250 stroke patients who were undergoing neurorehabilitation. These patients received a combination of co-ultramicronized PEA (700 mg) and luteolin (70 mg) daily for 60 days.<sup>28</sup> The study reported significant improvements across a broad range of domains, including neurological status, muscle spasticity, pain, and, importantly, independence in activities of daily living.

One of the most striking findings was the measurable improvement in cognitive function. The average score on the Mini-Mental State Examination (MMSE), a standard test of cognition, increased from 20.2 to 22.7 within just 30 days of treatment—a clinically meaningful gain.<sup>28</sup> Another clinical trial involving patients with acute ischemic stroke found that adding PEA supplementation to standard thrombolytic therapy resulted in "significantly better recovery and cognitive improvement" compared to standard therapy alone.<sup>28</sup> Furthermore, a smaller study of 20 post-stroke patients suffering from pain and spasticity found that adding PEA (600 mg twice daily) to their rehabilitation regimen significantly reduced both pain intensity and spasticity.<sup>28</sup>

While these results are highly encouraging, it is important to note a major caveat: the largest study was open-label in design.<sup>22</sup> This means that both patients and investigators were aware of the treatment being administered. Because stroke patients typically show some degree of spontaneous functional improvement over time, the lack of a placebo control group makes it difficult to definitively attribute all of the observed benefits to the PEA-LUT intervention. Nonetheless, the magnitude and breadth of the reported improvements, especially the rapid cognitive gains, are notable and warrant confirmation in rigorous, placebo-controlled trials.

### **3.3 Parkinson's Disease (PD): Adjuvant Therapy with Striking Potential**

Parkinson's disease is a progressive neurodegenerative disorder characterized by motor symptoms like tremor and stiffness, as well as debilitating non-motor symptoms such as depression, fatigue, and cognitive dysfunction. While levodopa remains the gold standard for managing motor symptoms, it does not halt disease progression. Evidence from an observational study suggests that ultramicronized PEA (um-PEA), when used as an add-on therapy, may have a profound impact on the course of the

disease.

The most extraordinary finding comes from a 2017 study by Brotini and colleagues, which followed PD patients on stable levodopa therapy who were given adjuvant um-PEA (1200 mg/day for three months, then 600 mg/day for up to a year).<sup>17</sup> The severity of Parkinson's was measured using the Hoehn and Yahr (HY) scale. In the months leading up to the trial, the patients' collective HY score showed the expected disease progression, worsening from 1.8 to 2.5. However, after one year of continuous um-PEA therapy, their collective HY score had improved to 1.9.<sup>17</sup> This result is remarkable because it suggests not just a slowing of progression, but a near-reversal of the decline that had occurred in the previous year. Standard PD therapies manage symptoms but do not typically reverse measured disease severity in this way.

This potential disease-modifying effect was accompanied by broad symptomatic benefits. The study reported that adjuvant um-PEA led to significantly improved motor symptoms, better performance in activities of daily living, and significant improvements in crucial non-motor symptoms, including mood deficits, fatigue, sleep disturbances, and mental tasks, after one year of administration.<sup>28</sup> While these findings are from an observational study and not a randomized controlled trial, the magnitude of the reported effect on the HY scale is exceptional and, if replicated in a rigorous RCT, would represent a major breakthrough in the management of Parkinson's disease.

### **3.4 Amyotrophic Lateral Sclerosis (ALS): Delaying Inevitable Decline**

Amyotrophic Lateral Sclerosis is a relentlessly progressive and universally fatal neurodegenerative disease that destroys motor neurons, leading to muscle weakness, paralysis, and eventual respiratory failure. In a disease with such a grim prognosis, therapies that can even modestly slow the decline are of immense clinical value. Preliminary evidence suggests that ultramicroinjected PEA (um-PEA) may offer such a benefit.

While much of the initial evidence comes from case reports showing that um-PEA led to rapid and notable improvements in muscle force, respiratory efficacy, and daily living activities<sup>28</sup>, a "larger study" pointed to more profound effects. This study found that PEA treatment resulted in a slower decline in respiratory function in ALS patients.

Critically, the treatment was also found to have

**delayed the need for tracheotomy and death.<sup>28</sup>**

These are hard, unambiguous clinical endpoints. In a disease like ALS, where the primary cause of mortality is respiratory failure, slowing the decline of lung function and delaying the need for invasive mechanical ventilation are profoundly meaningful outcomes for both patients and their families. While this evidence is not yet from a large-scale RCT, it provides a strong signal that PEA's neuroprotective and anti-inflammatory mechanisms may be able to impact the devastating trajectory of ALS.

### **3.5 Mild Cognitive Impairment (MCI): A Glimpse of Normalization**

Mild Cognitive Impairment, particularly the amnestic type, is often a transitional state preceding the onset of Alzheimer's disease. Intervening at this early stage is a key goal of dementia research. While large-scale trial data is lacking, an exceptionally compelling single case study highlights the potential of PEA-LUT in this population.

The case involved an elderly female patient with amnestic-MCI who was treated with PEA-LUT therapy for nine months.<sup>28</sup> The results were profound. Clinically, she experienced a "significant improvement in cognitive performance" to the point where her formal neuropsychological evaluation became

"almost normal".<sup>28</sup>

What makes this case particularly remarkable is the presence of objective, physiological evidence that corroborates the clinical improvement. The patient underwent single-photon emission computed tomography (SPECT) brain imaging, a technique that measures regional cerebral blood flow and metabolism. Before treatment, her scan showed hypometabolism (reduced activity) in brain regions typically affected in MCI. After nine months of PEA-LUT therapy, a follow-up SPECT scan showed "**normalized hypometabolism**".<sup>9</sup> The convergence of a dramatic clinical recovery with the normalization of an objective neuroimaging biomarker is exceptionally powerful. While it is only a single case, this result strongly suggests that PEA-LUT may be capable of reversing the underlying metabolic dysfunction associated with early-stage neurodegeneration and creates an urgent imperative for

larger-scale investigation in MCI and early AD populations.

### **3.6 Alzheimer's Disease (AD): Strong Preclinical Rationale, Awaiting Human Data**

Alzheimer's disease is the most common cause of dementia worldwide. Despite decades of research, therapeutic options remain limited. The preclinical evidence supporting the use of PEA for AD is extensive and highly compelling, positioning it as a prime candidate for clinical translation.

Numerous studies in *in vitro* (cell culture) and *in vivo* (animal) models of AD have demonstrated PEA's neuroprotective effects.<sup>8</sup> In cell-based models, PEA has been shown to protect neurons from the toxic effects of the amyloid-beta (A $\beta$ ) peptide, preventing A $\beta$ -induced cell death and preserving the functionality of both neurons and astrocytes.<sup>19</sup>

The results from animal models are even more impressive. In transgenic mouse models of AD that develop amyloid plaques, tau tangles, and cognitive deficits, chronic oral administration of ultramicrocrystallized PEA (um-PEA) has been shown to:

- Rescue cognitive deficits in learning and memory tasks.<sup>30</sup>
- Ameliorate core neuropathological features by reducing the formation of A $\beta$  and the hyperphosphorylation of tau protein.<sup>30</sup>
- Restrain the key drivers of neurodegeneration by powerfully reducing neuroinflammation and oxidative stress.<sup>30</sup>

These beneficial effects are directly linked to PEA's known mechanisms, particularly the activation of PPAR- $\alpha$  and the modulation of glial cell activity.<sup>19</sup> Despite this wealth of promising and consistent preclinical data providing a strong rationale for its use, the available research contains

**no human clinical trial results for PEA in patients with Alzheimer's Disease.**<sup>28</sup> The scientific literature consistently concludes this section of research with the same refrain: "larger clinical trials are needed" to elucidate the role of PEA and PEA-LUT in AD treatment.<sup>28</sup> This represents the most significant gap in the current evidence base for PEA and the most critical area for future investigation.

## **Section 4: Synthesis of Remarkable Outcomes: Reclaiming Brain Function**

The term "remarkable" is often used in describing the effects of Palmitoylethanolamide, a descriptor justified by a collection of quantitative and objective findings that suggest a capacity not just to manage symptoms, but to preserve or even restore brain function in ways that are uncommon for currently available therapies. This section synthesizes the most impactful of these outcomes, illustrating the potential of PEA to alter the course of severe neurological diseases.

### **4.1 Slowing Progression in an Untreatable Disease (FTD)**

The most rigorously documented remarkable outcome comes from the Phase 2 RCT in Frontotemporal Dementia. The finding that PEA-LUT reduced the rate of global disease progression by over 50% compared to placebo (a mean change of 0.53 vs. 1.39 on the CDR-FTD-SoB scale over 24 weeks) is a standout result in the field of neurodegeneration.<sup>15</sup> For a devastating disease like FTD, which has no approved treatments and relentlessly strips individuals of their personality and function, a therapy that can significantly slow this decline represents a profound beacon of hope and a potential paradigm shift in its management.

### **4.2 Reversing Measured Disease Severity (PD)**

Perhaps the single most astonishing finding in the entire body of PEA literature is the observational data from the Parkinson's disease study. The Hoehn and Yahr (HY) scale is a standard measure of disease stage and severity. The observation that the collective HY score, after progressing from 1.8 to 2.5, subsequently improved to 1.9 following a year of adjuvant um-PEA therapy is extraordinary.<sup>17</sup> Standard PD therapies are designed to manage symptoms; they do not reverse the underlying progression as measured by staging scales. While this finding urgently requires confirmation in a randomized controlled trial, it hints at a deeply neuroprotective or even restorative

effect that is virtually unprecedented in PD therapeutics.

#### **4.3 Normalizing Brain Activity (MCI)**

The power of the Mild Cognitive Impairment case study lies in its combination of clinical and physiological data. The patient's cognitive improvement to an "almost normal" state is a remarkable outcome in itself.<sup>28</sup> However, it is the objective evidence from SPECT imaging that elevates this finding. The visualization of "normalized hypometabolism" provides a physiological correlate for the cognitive gains.<sup>9</sup> It suggests that the PEA-LUT treatment did not simply mask a deficit but may have helped to reverse the underlying metabolic brain dysfunction that is a hallmark of early neurodegeneration. This alignment of subjective improvement and objective biomarker normalization is a rare and powerful indicator of a true disease-modifying effect.

#### **4.4 Measurable Cognitive Gains (Stroke)**

In the context of post-stroke rehabilitation, regaining cognitive function is critical for a patient's independence and quality of life. The 2.5-point average increase on the 30-point MMSE scale observed within just 30 days in the 250-patient open-label study is a clinically significant improvement.<sup>28</sup> This rapid and substantial gain in global cognitive function, if confirmed in controlled trials, would position PEA-LUT as a valuable tool for accelerating and enhancing cognitive recovery during the crucial post-stroke period.

#### **4.5 Extending Life and Function (ALS)**

In a universally fatal disease like ALS, the most meaningful outcomes are those that impact survival and preserve essential functions. The finding from a larger study that PEA treatment could slow the decline of respiratory function and, consequently, delay the need for tracheotomy and death is of paramount importance.<sup>28</sup> These are hard,

unambiguous endpoints that directly address the primary cause of mortality in ALS. The ability to extend the time before a patient requires invasive ventilation represents a significant improvement in quality of life and a tangible impact on the relentless course of this disease.

## **Section 5: Critical Analysis, Safety Profile, and Future Imperatives**

While the therapeutic promise of Palmitoylethanolamide is considerable, a comprehensive assessment requires a critical analysis of the evidence, a thorough understanding of its safety profile, and a clear vision for the future research needed to translate this promise into clinical reality. PEA's unique combination of potential efficacy and high safety makes it a particularly compelling candidate for further development.

### **5.1 A Robust and Differentiated Safety Profile**

One of the most consistent and appealing attributes of PEA reported across the scientific literature is its exceptional safety and tolerability profile. In dozens of studies encompassing thousands of patients, PEA is consistently described as being very well-tolerated with a remarkably low rate of adverse events.<sup>9</sup>

A 2017 meta-analysis that examined the efficacy of PEA for pain found that the all-cause dropout rate was actually non-significantly *lower* in the groups receiving PEA compared to the inactive control groups.<sup>32</sup> This suggests that patients find the treatment highly tolerable, even more so than placebo in some cases. The reported side effects are typically mild and infrequent, with some trials noting minor gastrointestinal upset or drowsiness.<sup>32</sup> This high degree of safety has been observed even with long-term administration over many months.

This robust safety profile is not incidental; it is likely a direct consequence of PEA's fundamental mechanism of action. As an ALIAmide, PEA functions as a homeostatic regulator, gently modulating and enhancing the body's own protective and anti-inflammatory systems rather than acting as a potent agonist or antagonist of a single pathway. This approach is inherently less likely to cause the system-wide

imbalances and off-target effects that often plague conventional pharmaceutical agents. This intrinsic safety makes PEA particularly well-suited for potential long-term, chronic use in the management of neurodegenerative diseases, where treatment may be required for years or even decades.

## **5.2 Bridging the Preclinical-Clinical Gap and Acknowledging Limitations**

While the excitement surrounding PEA is warranted, it must be tempered by a sober acknowledgment of the current evidence's limitations. The quality and strength of the data vary significantly across different conditions. The evidence for FTD, derived from a Phase 2 randomized, double-blind, placebo-controlled trial, currently meets the highest standards of modern clinical research.<sup>15</sup>

However, for other conditions, the evidence, while compelling, is less rigorous. The large stroke study was open-label, making it susceptible to bias.<sup>22</sup> The truly remarkable findings in Parkinson's disease and Mild Cognitive Impairment are derived from an observational study and a single case report, respectively.<sup>17</sup> While these study designs are invaluable for generating hypotheses and identifying powerful signals of efficacy, they cannot replace the definitive evidence provided by an RCT.

The most significant gap exists for Alzheimer's disease. Despite an extensive and robust body of preclinical data demonstrating profound neuroprotective effects in animal models, there is a complete absence of human clinical trial data.<sup>28</sup> This preclinical-clinical gap is the single most important hurdle that needs to be overcome for AD. It is therefore crucial to avoid overstating the current evidence. While the collective data is highly suggestive of a broad neuroprotective potential, a nuanced, condition-specific approach is essential.

## **5.3 A Clear Path Forward: Recommendations for Future Research**

The consistent call across nearly every research paper, review, and meta-analysis on PEA is for more and better research to confirm the initial promising results.<sup>22</sup> The existing evidence base provides a clear and logical roadmap for the next phase of clinical investigation. The following recommendations outline a path to rigorously

validate PEA's therapeutic potential:

- **For Frontotemporal Dementia (FTD):** Based on the successful and highly significant results of the Phase 2 trial, the immediate and logical next step is to design and initiate a larger, multicenter Phase 3 registration trial. Such a trial would be intended to confirm the disease-modifying effects on a larger scale and could form the basis for regulatory approval.
- **For Parkinson's Disease (PD), Stroke, Mild Cognitive Impairment (MCI), and Amyotrophic Lateral Sclerosis (ALS):** For this group of conditions, the priority is to move beyond observational, open-label, and case-study evidence. It is imperative to design and conduct large-scale, double-blind, placebo-controlled randomized trials to rigorously test the remarkable but preliminary findings. These trials should aim to replicate the specific outcomes reported, such as the improvement in the HY scale for PD, the normalization of SPECT imaging for MCI, and the delay of hard endpoints for ALS.
- **For Alzheimer's Disease (AD):** The time is now ripe to bridge the preclinical-clinical gap. The wealth of strong preclinical data provides an unequivocal rationale to initiate the first human pilot studies (Phase 1/2 trials) in patients with MCI or early-stage AD. These initial trials should focus on confirming safety and tolerability in this population, establishing optimal dosing, and, crucially, incorporating biomarker analysis (e.g., neuroinflammatory markers in cerebrospinal fluid, amyloid and tau PET imaging) to see if the mechanisms observed in animals translate to humans.

Across all future trials, it is essential that studies utilize optimized, bioavailable formulations such as ultramicronized PEA (um-PEA) or the synergistic co-ultramicronized PEA-luteolin (PEA-LUT), as these are the formulations that have produced the most significant results. By pursuing this evidence-based research agenda, the scientific community can work to definitively establish the role of this fascinating endogenous molecule in the future treatment of age-related and neurodegenerative brain conditions.

## Works cited

1. Palmitoylethanolamide and White Matter Lesions: Evidence for Therapeutic Implications, accessed June 14, 2025, <https://www.mdpi.com/2218-273X/12/9/1191>
2. Palmitoylethanolamide and White Matter Lesions - Encyclopedia.pub, accessed June 14, 2025, <https://encyclopedia.pub/entry/27252>
3. The search for the palmitoylethanolamide receptor - eScholarship.org, accessed June 14, 2025, [https://escholarship.org/content/qt4bg0t44t/qt4bg0t44t\\_noSplash\\_dea9f99e9d7](https://escholarship.org/content/qt4bg0t44t/qt4bg0t44t_noSplash_dea9f99e9d7)

[f2a1015bb70be833126c3.pdf?t=ovhx7t](#)

4. Get to Know PEA and Its History - Metagenics Blog, accessed June 14, 2025, <https://blog.metagenics.com/post/2019/10/17/get-to-know-pea-and-its-history/>
5. Therapeutic Use of Palmitoylethanolamide as an Anti-Inflammatory and Immunomodulator, accessed June 14, 2025, <https://www.mdpi.com/2673-9879/3/4/58>
6. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations - PubMed Central, accessed June 14, 2025, <https://PMC.ncbi.nlm.nih.gov/articles/PMC5429331/>
7. Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A Review from Rodents to Humans - ResearchGate, accessed June 14, 2025, [https://www.researchgate.net/publication/360404264\\_Effects\\_of\\_Palmitoylethanolamide\\_on\\_Neurodegenerative\\_Diseases\\_A\\_Review\\_from\\_Rodents\\_to\\_Humans](https://www.researchgate.net/publication/360404264_Effects_of_Palmitoylethanolamide_on_Neurodegenerative_Diseases_A_Review_from_Rodents_to_Humans)
8. Effects of Palmitoylethanolamide on Neurodegenerative Diseases: A ..., accessed June 14, 2025, <https://www.mdpi.com/2218-273X/12/5/667>
9. Palmitoylethanolamide (PEA) as a Potential Therapeutic Agent in Alzheimer's Disease, accessed June 14, 2025, <https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2019.00821/full>
10. Effects of Palmitoylethanolamide on Neurodegenerative Diseases - Encyclopedia.pub, accessed June 14, 2025, <https://encyclopedia.pub/entry/23010>
11. Palmitoylethanolamide - Wikipedia, accessed June 14, 2025, <https://en.wikipedia.org/wiki/Palmitoylethanolamide>
12. Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and - Semantic Scholar, accessed June 14, 2025, <https://pdfs.semanticscholar.org/b7b1/e443e898638702bc6de8f0e328b231fd03f5.pdf>
13. Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and Analgesic Compound | OMICS International, accessed June 14, 2025, <https://www.omicsonline.org/open-access/professor-rita-levi-montalcini-on-nerve-growth-factor-mast-cells-and-palmitoylethanolamide-an-endogenous-anti-inflammatory-and-analgesic-compound-2167-0846.1000114.php?aid=12372>
14. Pain & Relief Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and Analgesic Compound - ResearchGate, accessed June 14, 2025, [https://www.researchgate.net/publication/248399841\\_Pain\\_Relief\\_Professor\\_Rita\\_Levi-Montalcini\\_on\\_Nerve\\_Growth\\_Factor\\_Mast\\_Cells\\_and\\_Palmitoylethanolamide\\_an\\_Endogenous\\_Anti-Inflammatory\\_and\\_Analgesic\\_Compound](https://www.researchgate.net/publication/248399841_Pain_Relief_Professor_Rita_Levi-Montalcini_on_Nerve_Growth_Factor_Mast_Cells_and_Palmitoylethanolamide_an_Endogenous_Anti-Inflammatory_and_Analgesic_Compound)
15. Phase 2 study of palmitoylethanolamide combined with luteoline in ..., accessed June 14, 2025, <https://academic.oup.com/braincomms/article/7/2/fcaf080/8052642>
16. Palmitoylethanolamide: A Multifunctional Molecule for Neuroprotection, Chronic Pain, and Immune Modulation - MDPI, accessed June 14, 2025,

<https://www.mdpi.com/2227-9059/13/6/1271>

17. Update on Palmitoylethanolamide (PEA) for the Treatment of ..., accessed June 14, 2025,  
<https://journeywithparkinsons.com/2022/12/07/update-on-palmitoylethanolamide-pea-for-the-treatment-of-parkinsons/>
18. Oral Ultramicronized Palmitoylethanolamide: Plasma and Tissue Levels and Spinal Anti-hyperalgesic Effect - Frontiers, accessed June 14, 2025,  
<https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2018.00249/full>
19. Therapeutic effect of palmitoylethanolamide in cognitive decline: A systematic review and preliminary meta-analysis of preclinical and clinical evidence - PubMed Central, accessed June 14, 2025,  
<https://pmc.ncbi.nlm.nih.gov/articles/PMC9650099/>
20. Therapeutic effect of palmitoylethanolamide in cognitive decline: A systematic review and preliminary meta-analysis of preclinical and clinical evidence - PubMed, accessed June 14, 2025, <https://pubmed.ncbi.nlm.nih.gov/36387000/>
21. Palmitoylethanolamide: A Nutritional Approach to Keep ... - MDPI, accessed June 14, 2025, <https://www.mdpi.com/1422-0067/21/24/9526>
22. Palmitoylethanolamide (PEA) - Alzheimer's Drug Discovery Foundation, accessed June 14, 2025,  
[https://www.alzdiscovery.org/uploads/cognitive\\_vitality\\_media/Palmitoylethanolamide-Cognitive-Vitality-For-Researchers.pdf](https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Palmitoylethanolamide-Cognitive-Vitality-For-Researchers.pdf)
23. Therapeutic effect of palmitoylethanolamide in cognitive ... - Frontiers, accessed June 14, 2025,  
<https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyg.2022.103812/full>
24. Therapeutic effect of palmitoylethanolamide in cognitive decline: A systematic review and preliminary meta-analysis of preclinical and clinical evidence - ResearchGate, accessed June 14, 2025,  
[https://www.researchgate.net/publication/364818301\\_Therapeutic\\_effect\\_of\\_palmitoylethanolamide\\_in\\_cognitive\\_decline\\_A\\_systematic\\_review\\_and\\_preliminary\\_meta-analysis\\_of\\_preclinical\\_and\\_clinical\\_evidence](https://www.researchgate.net/publication/364818301_Therapeutic_effect_of_palmitoylethanolamide_in_cognitive_decline_A_systematic_review_and_preliminary_meta-analysis_of_preclinical_and_clinical_evidence)
25. Therapeutic effect of palmitoylethanolamide in cognitive decline: A systematic review and preliminary meta-analysis of preclinic - UNIUD, accessed June 14, 2025,  
<https://air.uniud.it/retrieve/245ef6da-f48c-4ff1-87d1-85fb8388bc52/fpsyg-13-103812.pdf>
26. Role of N-Acylethanolamines in the Neuroinflammation: Ultramicronized Palmitoylethanolamide in the Relief of Chronic Pain and Neurodegenerative Diseases - Neuropsychiatry (London), accessed June 14, 2025,  
<https://www.jneuropsychiatry.org/peer-review/role-of-nacylethanolamines-in-the-neuroinflammation-ultramicronized-palmitoylethanolamide-in-the-relief-of-chronic-pain-and-neurod-12915.html>
27. Role of N-Acylethanolamines in the Neuroinflammation: Ultramicronized Palmitoylethanolamide in the Relief of Chronic Pain and Neurodegenerative

- Diseases - Neuropsychiatry (London), accessed June 14, 2025,  
<https://www.jneuropsychiatry.org/peer-review/role-of-nacylethanolamines-in-the-neuroinflammation-ultramicronized-palmitoylethanolamide-in-the-relief-of.pdf>
28. PEA Restores Leptin Sensitivity in Ovariectomized Rats - NotebookLM -  
[https://notebooklm.google.com\\_.pdf](https://notebooklm.google.com_.pdf)
29. The Association of Palmitoylethanolamide with Luteolin Decreases Neuroinflammation and Stimulates Autophagy in Parkinson's Disease Model | Request PDF - ResearchGate, accessed June 14, 2025,  
[https://www.researchgate.net/publication/281167318\\_The\\_Association\\_of\\_Palmitoylethanolamide\\_with\\_Luteolin\\_Decreases\\_Neuroinflammation\\_and\\_Stimulates\\_Autophagy\\_in\\_Parkinson's\\_Disease\\_Model](https://www.researchgate.net/publication/281167318_The_Association_of_Palmitoylethanolamide_with_Luteolin_Decreases_Neuroinflammation_and_Stimulates_Autophagy_in_Parkinson's_Disease_Model)
30. Chronic Oral Palmitoylethanolamide Administration Rescues Cognitive Deficit and Reduces Neuroinflammation, Oxidative - Semantic Scholar, accessed June 14, 2025,  
<https://pdfs.semanticscholar.org/5e9b/5f51e4c83e37b82bcc0e061fcbd9f0df0520.pdf>
31. Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation | Arteriosclerosis, Thrombosis, and Vascular Biology, accessed June 14, 2025,  
<https://www.ahajournals.org/doi/10.1161/ATVBAHA.118.311185>
32. Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis, accessed June 14, 2025,  
<https://www.painphysicianjournal.com/current/pdf?article=NDUwMg%3D%3D&journal=106>
33. Formulated Palmitoylethanolamide Supplementation Improves Parameters of Cognitive Function and BDNF Levels in Young, Healthy Adults: A Randomised Cross-Over Trial - MDPI, accessed June 14, 2025,  
<https://www.mdpi.com/2072-6643/16/4/489>
34. palmitoylethanolamide (pea), accessed June 14, 2025,  
[https://goodmedicine.org.uk/sites/default/files/pea\\_0.pdf](https://goodmedicine.org.uk/sites/default/files/pea_0.pdf)