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# The Growing Evidence for Photobiomodulation as a Promising Treatment for Alzheimer's Disease

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## Abstract

Despite the current belief that there is no effective treatment for Alzheimer's Disease (AD), one emerging modality may change this belief: Photobiomodulation (PBM). It has credible mechanisms and growing evidence to support its case. Transcranial PBM for AD is a single intervention with multiple pathway mechanisms stemming from delivering low energy near infrared (NIR) light to the mitochondria in brain cells. The mechanisms involve the activation of gene transcription that lead to neuronal recovery, removal of toxic plaques, normalizing network oscillations that can lead to improved cognition and functionality. When PBM is delivered at 810 nm wavelength and pulsed at 40 Hz, early evidence suggests that very significant outcomes are possible. Literature related to PBM and AD has covered in vitro cellular, animal and human case reports, with promising results. They warrant robust randomized trials which are either ongoing or ready to start. The evidence in human studies is manifested in assessment scales such ADAS-cog, MMSE, and ADAS-ADL, and are supported by fMRI imaging and EEG.

## Keywords

Photobiomodulation, Alzheimer's Disease, Near Infrared Light, Default Mode Network, Clinical Trials, A$\beta$, Neurofibrillary Tangles, Tau, Neuro Gamma

## 1. Introduction

It is widely accepted that there is no effective treatment for Alzheimer's disease (AD). More than 99 percent of drug trials have failed [1]. In the meantime, about 47 million people around the world are suspected to have the disease.

General expectations for an effective treatment are pharmacological, targeting a single protein. However, AD has a complex etiology, involving the actions of genes, $\beta$-amyloid, tau oligomers, as well as other proposed pathology such as a herpes virus, microbiome or diabetes. It is now widely accepted that no single drug can be the solution—requiring a cocktail combination, and largely hypothesizing that the disease should be addressed at the pre-symptomatic or prodromal stages [2].

In the midst of the conundrum for an AD treatment, a new modality is slowly building evidence to support its case as a credible therapy: transcranial Photobiomodulation (PBM), which involves the delivery of near infrared (NIR) light into the brain. The fundamental mechanism is understood to be in the modulation of mitochondrial activity, which will be the hypothetical basis for the effectiveness of PBM to address AD. This manuscript will be a discussion about how PBM has the bases to improve AD conditions and the accumulated related evidence to support this proposition at the time of writing.

## 2. Pathophysiology to Target

### 2.1. Beta-Amyloid, Neurofibrillary Tangles and Related Proteins

The amyloid cascade hypothesis has been the dominant hypothesis over the last decades. Patients with AD have a build-up of amyloid-$\beta$ (A$\beta$) in their brains, which form the senile plaques, widely recognized as a pathological hallmark of AD. They stem from mutations in the amyloid precursor protein (APP) [3] and the genes that form the secretase enzymes that cleave APP [4]. When APP is sequentially cleaved by $\beta$-secretase and then $\gamma$-secretase, the formation of A$\beta$ occurs. The gene, apolipoprotein E (ApoE) type 4 has been identified as the most significant known risk factor for AD [5]. A$\beta$ plaques contain other proteins which encompass and infiltrate the plaques. These proteins include proteins found in astrocytes, microglia, dystrophic neuritis and amyloid binding proteins (*i.e.* ubiquitin, apolipoprotein E and clusterin). Some drugs were able to remove some of the amyloid plaque load, which did not translate into an improvement in symptoms of AD [6] [7] [8] [9].

Neurofibrillary tangles (NFT) are also characteristic of the pathology of AD. These proteins self-aggregate to become insoluble forms filaments, increasingly recognized as a major factor in AD pathology. The accumulation of tau in the neurons begins prior to the formation of NFT, suggesting that there is an early imbalance in the protein activity in AD [10]. NFT have been found to contain tau binding proteins (*i.e.* cytoskeletal proteins, kinases and heat shock proteins) [11]. Several drug trials have focused on tau-based targets, including tau protein, tau phosphorylation, tau oligomerization, tau degradation and tau-based vaccination. To date, none of these trials have been successful.

### 2.2. The Futility of Single-Protein Targeting

No new Alzheimer's therapies having gained US Food and Drug Administration

(FDA) approval since 2003 [1]. Pharmacotherapies have largely focused on specific targets in various proteins and enzymes underlying various pathological pathways in AD. However, it has clearly been established that the pathophysiology of Alzheimer's disease is complex with multiple protein pathogeneses. Therefore, success is likely only offered to multitargeting cocktail of drugs. The success of single-targeting drug has already proven daunting. Given this, the prospect of successful combination has almost impossible odds. This has never been admitted by researchers but there is some admission that multi-drug therapy is required for success, or given the slim chance of success of this strategy, research should now focus on prevention, attempting to catch the disease at the early biochemical phase [2].

### 2.3. Going More Basic to Target the Mitochondria

The mitochondria are vital to neuronal function as they supply cellular energy, in the form of adenosine triphosphate (ATP). Mitochondrial dysfunctions are well documented in the brains of patients with AD [12] [13]. Their dysfunction is a major cause for deficits in cerebral glucose metabolism that occurs in the brains of patients with AD associated with memory such as the hippocampus and entorhinal cortex [14]. The deficits occur well in advance of presentations of the clinical symptoms. Mitochondrial dysfunctions observed in AD are expressed as decreased mitochondrial enzyme activity, decreased activity of complexes of the respiratory chain and excessive levels of reactive oxygen species (ROS), producing increased oxidative stress.

The reductions in energy metabolism, increased oxidative stress and synaptic dysfunction embody a common final pathway of all risk factors (genetic and non-genetic) for the development of AD [12] [15] [16], leading to the development of the mitochondrial cascade hypothesis. It has been demonstrated that mitochondrial dysfunction can push APP processing towards the formation of A$\beta$ production [17] [18] [19], suggesting that mitochondrial dysfunction is a factor driving the amyloid cascade resulting in further damage to mitochondria, leading to a self-feeding feedback loop. Overall, this leads to an increase in the production of A$\beta$ and further mitochondrial damage. It has been suggested that mitochondrial dysfunction is the leading pathomechanism that causes neurodegeneration and AD-associated deficits [9].

In summary, restoring optimum mitochondrial function could help to overcome the complex pathology of AD, including the elements that involve A$\beta$ and NFT formations. Thus, there is a need to identify a therapy that is effective at treating mitochondrial dysfunction. Photobiomodulation could be the intervention that meets this need.

### 2.4. Photobiomodulation Modulates Mitochondrial Function

Photobiomodulation (PBM), also known as low-level light therapy (LLLT), is a biostimulation technique that shows promise in treating a number of conditions,

including dementia and Alzheimer's disease. The most well investigated mechanism of action of PBM is its fundamental effect on mitochondrial function [20]. The process increases the amount of ATP produced, as well as cyclic adenosine monophosphate (cAMP) and reactive oxygen species (ROS) [21].

The increase in ATP increases the activity of ion channels, regulate cAMP and calcium, which results in the stimulation of diverse biological cascades [22] [23] and activate up to 110 genes, which themselves lead to the prolongation of the production of energy by the mitochondria [24].

The increase of ROS formation is transient and at low levels. This is thought to activate mitochondrial signalling pathways that have antioxidant, anti-apoptotic and cytoprotective effects on cells [25]. A number of cellular mechanisms are in involved in sensing excessive levels of ROS, and respond by activating transcription factors which produce increased antioxidant defenses, preserving homeostasis [26].

In addition to increasing levels of ATP and cAMP, it has been observed that PBM results in an increase in nitric oxide (NO) levels, dissociated from the mitochondria where the photons are absorbed [20] [27]. The dissociation of NO from cytochrome c oxidase (CCO) leads to the further enhancement of ATP production and acts as a vasodilator as well as a dilator of lymphatic flow, and can signal to activate a number of beneficial cellular pathways [20] [23].

The points raised here support PBM as a promising therapy for AD, and it now comes to how to put theory into practice.

## 3. The Progress of Clinical Evidence with Photobiomodulation

Early investigations on the effect on PBM on brain cells began with in vitro experiments, demonstrating the impressive regenerative quality of damaged neurites. It is the changes in the AD biomarkers and behavior of living mammals that suggest the promises of PBM as a treatment for the disease.

### 3.1. Evidence with Animal Models

Recently, the media headlined a report that that by reducing the level of the enzyme $\beta$-site amyloid precursor protein cleaving enzyme 1 (BACE1) through genetic modification in mice as they aged, either prevented or reversed the formation of amyloid plaques in the brain [28]. However, a few years ago, PBM produced similar results in an animal study without gaining the same level of attention. This study produced a reduction in the amyloid-$\beta$ peptide neuropathology in a mice model of AD in response to near-infrared PBM, which was reported by De Taboada *et al.* 6 years earlier. Administration of transcranial laser therapy of 808 nm wavelength three times/week at various doses to an amyloid $\beta$ protein precursor on the transgenic mouse model from three months of age, resulted in a significant reduction in amyloid load and improved behaviour [29]. Expression of inflammatory markers was reduced, producing a decrease in the activity of $\beta$-secretase, leading to reduced A$\beta$ plaque count.

More recently, PBM delivery of 670 nm light to the skull of two different mouse models of AD resulted in a reduction in AD-related neuropathology in the cerebral cortex [30]. PBM treatment decreased levels of hyperphosphorylated tau, neurofibrillary tangles and markers of oxidative stress in the neocortex and hippocampus, and a decrease in the number and size of the A$\beta$ plaques.

Findings from these studies warranted human clinical studies for PBM to treat AD as the next stage of investigations.

### 3.2. Human Clinical Studies with Photobiomodulation on Dementia

Human studies involving PBM on dementia and AD subjects are relatively recent. At the time of this writing, the following studies have been published:

- Saltmarche A *et al.*, 2017, involving five participants assessed over 12 weeks in a case series report presenting significant improvement using transcranial and intranasal PBM device, "Vielight Neuro" which used 810 nm wavelength and pulsed at 10 Hz [31]. The device used targeted the default mode network as shown in **Figure 1**.
- Berman M *et al.*, 2017, assessed 11 subjects with a transcranial PBM helmet over a short period of 28 days with some tests and electroencephalogram (EEG) readings that the authors interpret as improvement trends [32].
- Zomorrodi R *et al.*, 2017, reported on a moderately impaired AD case over 12 weeks who presented significant improvement in cognition within days, along with significant changes in EEG measures [33]. For the first time, PBM was delivered at 810 nm wavelength and pulsed at 40 Hz, which was to become the standard for future AD studies using "Vielight Neuro Gamma" device.

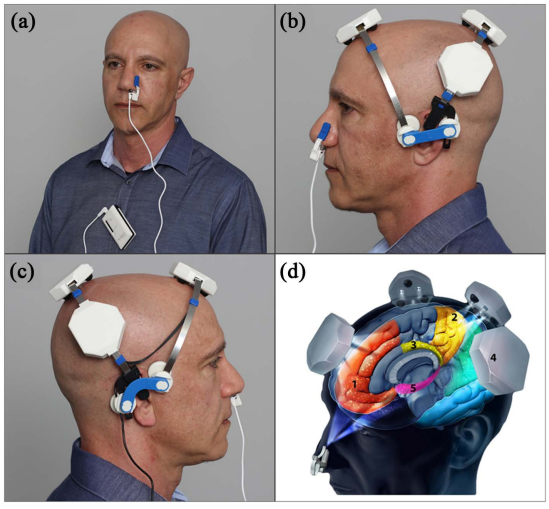


**Figure 1.** Photographs of Vielight "810" and "Neuro" illustrating correct device positions for treatment, and corresponding targeted network hubs. (a) Vielight "810"; (b) Vielight "Neuro", left view; (c) Vielight "Neuro", right view; (d) Targeted Default Network Nodes: 1) Mesial prefrontal cortex; 2) Precuneus; 3) Posterior cingulate cortex; 4) Inferior parietal lobe; 5) Hippocampus.

- Chao LL, University of California, San Francisco, applying measures of cognitive, Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), behavioral Neuropsychiatric Inventory (NPI), 3 Tesla resting state functional and Arterial Spin Labeling (ASL) and perfusion magnetic resonance imaging (MRI) on eight participants with dementia using the Vielight Neuro Gamma [34].

The following studies have been registered with the clinicaltrials.gov website and are ongoing at the time of writing as at 31 March 2018:

- Lim L *et al.*, Vielight Inc, in a randomized double-blind pilot study involving 60 moderate to severe AD participants over 12 weeks, applying the Severe Impairment Battery (SIB) scale as the primary endpoint, along with Alzheimer's Disease Cooperative Study—Activities of Daily Living for Severe Alzheimer's Disease (ADCS-ADL-Sev) and Neuropsychiatric Inventory (NPI) as secondary endpoints. Two Vielight Neuro RX Gamma versions that pulse in-synchrony and asynchrony are used in the study [35].

The following is being mobilized to commence in early 2019:

- Fischer C *et al.*, St. Michael's Hospital, Toronto, in a randomized double-blind pivotal study involving 228 patients with moderate to severe AD over eight sites with a duration of six months for each patient. The main primary and secondary endpoints are similar to the ongoing pilot study above. The asynchronous pulsing Vielight Neuro RX Gamma will be used in the study.
- Chao LL and Rojas RC. University of California, San Francisco, in a sham-controlled pilot study of 14 patients with biomarker confirmed diagnoses of AD. The pilot study will have a duration of four months for patients randomized to active PBM and an optional four-months of open-label PBM use for patients randomized to sham PBM. The primary endpoints will be measures of cognitive and behavioral function. The secondary endpoints will be measures of fluid (*i.e.*, blood and cerebral spinal fluid) biomarkers of neuroinflammation, neurodegeneration, neurotrophic factors, and AD pathology (e.g., A$\beta$42, A$\beta$42/A$\beta$40, total- and hyperphosphorylated tau).The asynchronous pulsing Vielight Neuro RX Gamma will be used in the study.

#### 3.2.1. Discussion on the Clinical Studies

The results of the clinical have been promising to date. However, a PBM intervention is not ready to be considered an effective treatment for AD until it passes the same standard of investigation placed on the pharmacotherapy trials. Considering the expensive failures of pharmacotherapy trials, such a claim would be considered extraordinary, requiring to pass "gold-standard" tests. These tests would call for much larger number of participants, producing statistically significant results in double-blind studies. These factors have been partially incorporated into the ongoing pilot study sponsored by Vielight Inc. [35] and then into a pivotal trial with its primary clinical trial site at the St. Michael's Hospital in Toronto, also sponsored by Vielight Inc.

## 4. Parameters and Their Rationale

The combination of several parameters is likely to be the major contributors to the potential success of PBM to treat AD. They are beyond the basic principle of delivering NIR light to the mitochondria, and are incorporated in the later Vielight Gamma models of Vielight and in future models to treat AD. The scientific bases for incorporating these are presented below.

### 4.1. The Default Mode Network

The default mode network (DMN) is a large-scale brain network involved that is particularly active when the brain is in a state of wakeful rest. This network includes the mesial prefrontal cortex, the posterior cingulate cortex, the hippocampus, the precuneus, the inferior parietal lobe and the temporal lobe, as presented in **Figure 1(d)**. The DMN is involved with a number of cognitive functions, including autobiographical memory, memory consolidation, and self-referential thought [36]. This network is of particular relevance for AD as the mesial prefrontal cortex, the medial temporal lobe and particularly the hippocampus are involved in mediating episodic moment processing. In AD, an impairment in episodic memory is one of the first symptoms observed [37].

Significant disruptions in the DMN have been reported in patients with AD [37] [38] [39] [40] [41]. A correlation has been reported between the anatomical distribution of amyloid plaques, neurotrophy and alterations in glucose metabolism [42]. Given the significant role that the DMN plays in the pathophysiology of AD, this network represents an important neuroanatomical target for treatment with PBM.

### 4.2. Gamma Pulse Frequency at 40 Hz

It had been observed that aberrant increases in network excitability and compensatory inhibitory mechanisms in the hippocampus may contribute to A$\beta$-induced neurological deficits in mouse models [43]. EEG recordings in mouse models indicated network hypersynchrony, primarily during reduced gamma oscillatory activity. Restoring gamma oscillation may inhibit overactive synaptic activity and reduce hypersynchrony, memory deficits, and premature mortality—conditions associated with AD [44]. In individuals with AD, this phenomenon is associated with a risk for an increased formation of A$\beta$ protein associated with AD [45].

The gamma pulse frequency of 40 Hz has been demonstrated to attenuate A$\beta$ proteins production in the visual cortex of mice that were in environments illuminated with light pulsing at that rate [46]. The authors theorized that the 40 Hz pulse rate modify microglia into the non-inflammatory state that engulfs the unwanted A$\beta$ protein deposits. When 40 Hz pulsing light were optogenetically induced in the hippocampus, A$\beta$ peptide levels in the location also attenuated significantly. From the data we hypothesize that A$\beta$ is attenuated in the brain regions that process pulsed light at 40 Hz, and if we can target 40 Hz to the right

areas such as the DMN, it could be an impactful treatment for AD.

## 5. The Future of Photobiomodulation as a Treatment for Alzheimer's Disease

To date, the evidence we have observed from the use of PBM to treat AD has been significant and very promising as presented above. However, any claim that is considered as extraordinary such as this, needs evidence beyond reproach. The bar has been set by the efforts of drug companies in clinical trials. The quality of evidence required would call for pivotal randomized double-blind clinical trials. In this respect, the upcoming pivotal trial will be carefully watched. Successful data from the trial provides the long-awaited breakthrough in the search for an effective treatment for AD.

## Acknowledgements

I thank the investigators cited in this study, who took the risk of committing time and resources into clinical studies, to investigate the viability of using Vielight devices for AD when there was scant evidence that they would have amounted to anything. Some of the content here are from part of a book chapter that Genane Loheswaran and Reza Zomorrodi have helped to co-write.

## Conflicts of Interest

The author is the Founder & Chief Executive Officer of Vielight Inc., the manufacturers of the devices that provided much of the clinical evidence referenced in the paper.

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