

The Potential of Treating Alzheimer's disease with Intranasal Light Therapy

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Abstract

Alzheimer's disease is the only one among the top 10 diseases in the United States with deaths increasing. It is extremely debilitating to the families, and its vast economic cost urgently calls for an effective treatment. Yet to date, none has been found to be effective.

Intranasal light therapy offers a biophysical solution with sound scientific bases. It operates on the principle of *photobiomodulation*, a biological phenomenon that is gaining increasing recognition amongst cellular biologists and neurologists. The use of photobiomodulation for pain treatment, wound healing, skin rejuvenation and hair growth are becoming common place in clinical practice. There is increasing literature on neurological healing with the use of the transcranial light therapy method.

A fundamental principle of photobiomodulation is that cells with mitochondria that are not in homeostasis would enter into the process to restore homeostasis when exposed to low intensity light in the red to near infrared wavelengths. This is also observed for neurons under oxidative stress. If similar light energy can reach neurons that are degenerating, as in the case of Alzheimer's disease, we expect to observe a similar restorative response.

Many of the key regions of the brain that suffer degeneration and contribute to the early onset of Alzheimer's disease are located in the underside and middle parts of the brain. They are easily accessible from the nasal cavity, requiring less input energy and more certainty than if directed from the outside of the skull to achieve the same outcomes. This also allows a low cost and user-friendly device to be developed, resulting in this proposal for an intranasal light therapy device to treat this disease.

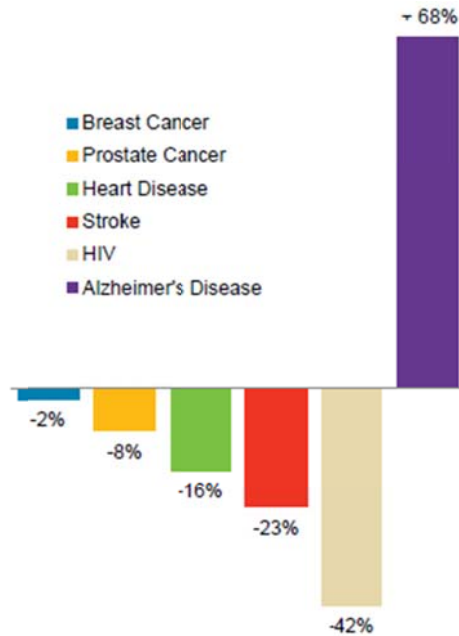
Based on literature and observed results, an effective offering is a low intensity light in the 810 nm near infrared (NIR) wavelength pulsing at 10 Hz. Energy in the region of 10 -15 mW/cm² delivered over 25 to 30 minutes, can deliver the necessary dosage. Early cases of human use are encouraging with consistent reports of significant improvements in Alzheimer's disease conditions with no adverse effects.

Based on an understanding of the scientific bases, various treatment protocols can be recommended. In the advanced stage where there is massive degeneration in the neocortex regions, a treatment that combines intranasal light therapy with the transcranial method could have added therapeutic effects.

Introduction

Modern medicine has contributed to the reversal in the growth of major diseases that include breast cancer, prostate cancer, heart disease, stroke and HIV. As the population lives longer, the one disease that has increased significantly is Alzheimer's disease (Figure 1).

Figure 1: Change in Number of Deaths between 2000 and 2010



Source: Alzheimer's Association

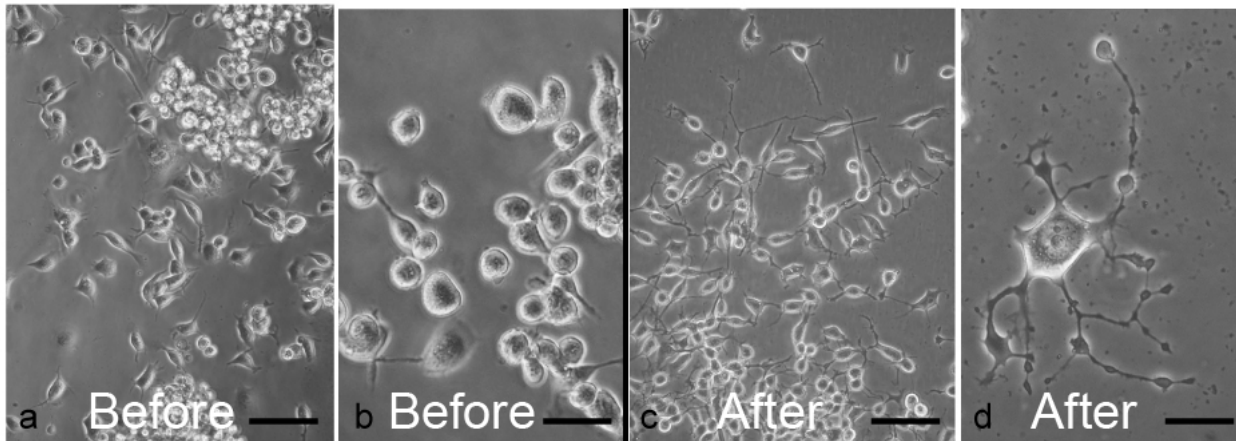
Alzheimer's disease is the only cause of death among the top 10 diseases in America without a way to prevent, cure or even slow its progression. Whilst deaths from the major diseases have decreased, including the number one cause of death (heart disease), deaths from Alzheimer's disease has increased 68 percent between 2000 and 2010.¹

In advanced stage Alzheimer's disease, the brain is shrunken due to neuron loss and neurodegeneration. If we could introduce an intervention that counters or slows this degenerative process, we may have a viable therapy for Alzheimer's disease. Most cells respond to light energy of low intensity in the red and near infrared red (NIR) spectrum, including neurons. Herein is the potential of low intensity light therapy, or *photobiomodulation*.

Cell repair and regeneration with photobiomodulation

Research shows that low energy light in the visible red and near infrared (NIR) stimulate cellular activity which activates healing processes resulting in wound healing,² skin rejuvenation,³ and in sports medicine for musculo-skeletal injuries and related pain.⁴ At cellular level, researchers found that cells repair themselves when exposed to photobiomodulation, as seen in Figure 2. Neurites of neurons that were shortened by oxidative stress would re-elongate.⁵

Figure 2: Neurite Elongation Experiment



In vitro post-oxidative stress. 670nm, 3 mW, 20 sec/day, 5 days [ref 5]

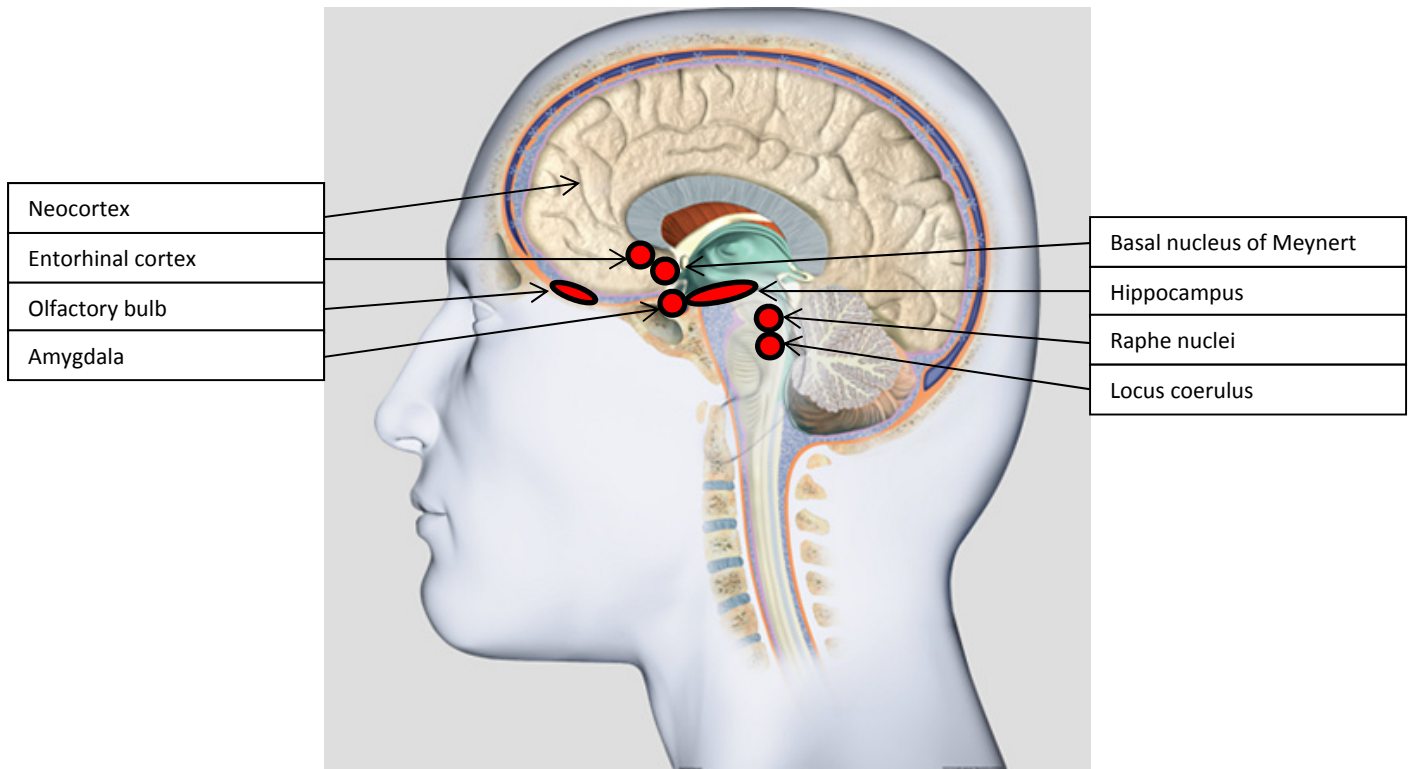
These studies point to a viable basis to support a proposal for light energy to arrest the progression or even reverse a degenerative disease such as Alzheimer's disease by irradiating the neurons. The neurons of Alzheimer's disease patients undergo a similar loss of neurites before they progress to full apoptosis or cell death; thus subjecting these cells with *neurobiostimulation* could stimulate healing.

The next step would be to identify the areas that are affected by the disease, and then propose a methodology to irradiate these areas with light energy of the appropriate parameters.

Areas of the brain impaired by Alzheimer's disease

The locations of the areas where the most pronounced neuron loss and dysfunction associated with Alzheimer's are shown in Figure 3.

Figure 3: Locations of neuron loss in Alzheimer's disease



Source of graphic: bodypartchart.com. Accessed August 22, 2013 (modified).
<http://www.bodypartchart.com/product/brain-cross-section/brain-cross-section-bpc-medium-image>

These locations, with a summary of their functions, are:

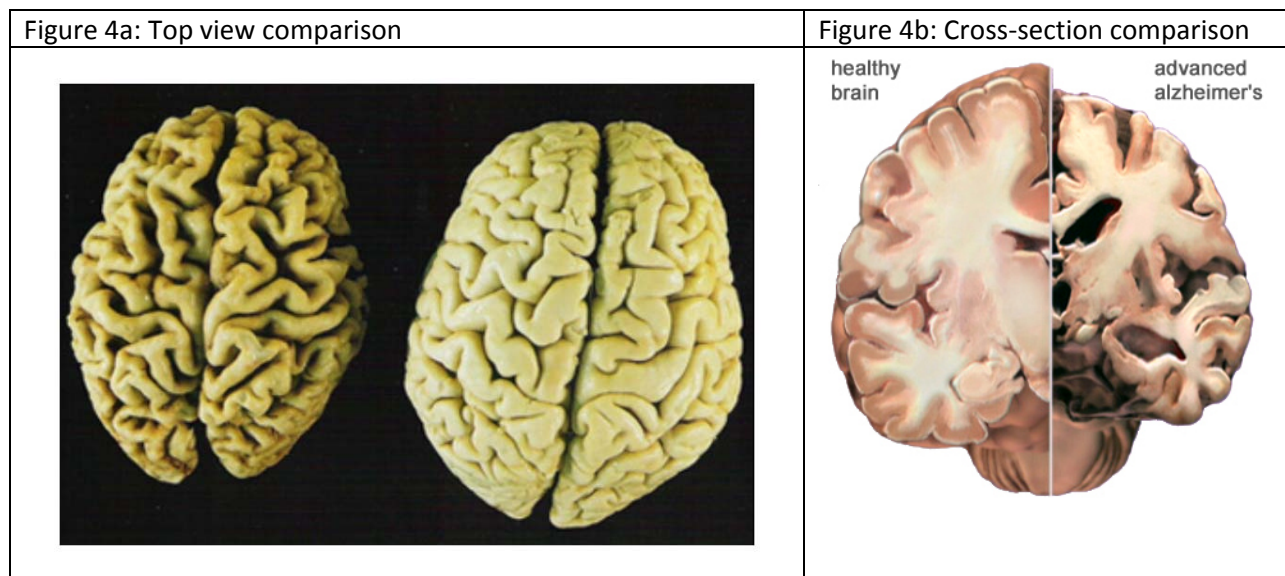
- *Neocortex*. These are the areas of higher order association. Advanced stage Alzheimer's disease is identified with massive loss in this region, resulting in the loss of the "person".
- *Entorhinal cortex* and *hippocampus*. Memory is dependent on the health of these areas covering episodic and autobiographical recollections, and spatial memory. These are the first areas to show abnormality in Alzheimer's disease.
- *Amygdala*. Emotions and fear are affected by the amygdala. With its degeneration, the patient fails to experience emotions normally.
- *Nucleus basalis of Meynert*. This is a small nucleus that supports the cortex with independent widespread projections that use acetylcholine as its neurotransmitter. It modulates the ratio of reality and virtual reality components of visual perception; and its degeneration is associated with dementia.
- *Nucleus locus coeruleus*. This is a small nucleus in the pons utilizing norepinephrine as a neurotransmitter. It also has independent widespread projections in the cortex and plays a role in the regulation of blood flow, extraction of oxygen and glucose in the brain, selective attention, the sleep cycle (circadian rhythm), and other functions.

- *Raphe nuclei*. These are groups of neurons spread throughout the brainstem using the neurotransmitter serotonin which is associated with managing depression. They also have massive independent projections to the cortex.
- *Olfactory bulb*. Olfaction dysfunction is also associated with Alzheimer's disease. These structures are high in acetylcholine, a neurotransmitter involved in the pathology of Alzheimer's disease and treatment. Some neuroscientists believe that the disease may also be caused by a pathogen entering the brain via olfactory pathways allowed by a dysfunctional olfactory bulb.

As most of the primal areas in the brain are essentially intact until the end stage of the disease, the patient's body is able to carry out life-sustaining functions but with significantly diminished control of voluntary thoughts and memory.

Autopsies of advanced Alzheimer's disease patients' brains show obvious neuron loss due to the degeneration in the neocortex. Massive neuron loss in this widespread region which covers the frontal, parietal and temporal lobes, results in higher order functions. However, by the time we witness this event, the other more primary regions identified above would have already suffered massive loss. See Figure 4a and 4b.

Figure 4a and 4b: Degeneration of the brain of an advanced Alzheimer's disease patient



Since cells that are subjected to photobiomodulation can heal, we could also infer that affected parts of the brain that are subjected to photobiomodulation to also heal. The question is how we can deliver this light to the affected areas of the brain.

Available methods of delivering photobiomodulation to the brain

There are two types of available commercial methods of delivering light energy to the human brain for therapeutic purposes:

1. Transcranial method
2. Intranasal method.

Transcranial light therapy as a delivery method

The transcranial light therapy method delivers light from outside the skull. It has been offered as a possible effective method of photobiomodulation to help with neurological conditions such as Alzheimer's and dementia. See Figure 5 below.

Figure 5: Transcranial light therapy in use



(source: <http://topnews.us/content/237119-transcranial-light-therapy-may-help-tbi-patients>)

Irradiating the brain from outside the skull should get light energy to the neurons in the neocortex as they are located close to the light source. Recent research, using laboratory mice, supports transcranial light therapy's potential for treating stroke, traumatic brain injury, Parkinson's disease, mild cognitive impairment, Alzheimer's disease, depression, and some other cognitive issues.⁶

However, the human brain is much larger than that of a mouse by many orders of magnitude. So the effect of a transcranial method with the same parameters may not be transferrable between mice and human beings. Bones and tissues scatter and attenuate light energy as it passes through the materials.⁷ It is therefore advantageous to have less bone and tissue barriers, and greater proximity between the light source and the targeted areas of degeneration, as it is for the intranasal method.

Intranasal light therapy as a delivery method

Intranasal light therapy as the name suggests, delivers light energy through inside the nose. This modality is the subject of this paper.

Researchers have linked the sleep-cycle hormone, melatonin to Alzheimer's disease. Melatonin secretion is decreased in Alzheimer's disease. Researchers have postulated that decreasing it could cause circadian disorganization, decrease in sleep efficiency and impaired cognitive function. This has been identified as "sundowning" which is identified by anxiety, fear, agitation and hallucinations. In 2002 study, Xu C et al divided the subjects into two groups, 47 patients with Alzheimer's disease and 22 patients with gastric ulcer, and treated the patients with red intranasal low level laser therapy at 3.5 - 4.5 mW for 30 minutes each time, done once every morning for 30 days. They found that melatonin and cognitive performance increased in the Alzheimer's disease group, but there was no significant change for the gastric ulcer group.

Alzheimer's disease is associated with widespread deposits of amyloid β plaques in the brain which may induce neurodegeneration. Since Alzheimer's disease is closely identified with neurodegeneration, a group of researchers experimented to see if light therapy would inhibit the degenerative process in neurons. Firstly, they induced apoptosis in the brain cells of rats with an amyloid β protein. Then they irradiated the neurons with LED of 640 nm wavelength at 0.09 mW/cm² for 60 minutes. The result showed that the process significantly diminished apoptosis. In a further experiment, they found that the same cells secreted anti-apoptosis factors that promoted further neuronal viability.

How the intranasal and transcranial methods can be effective

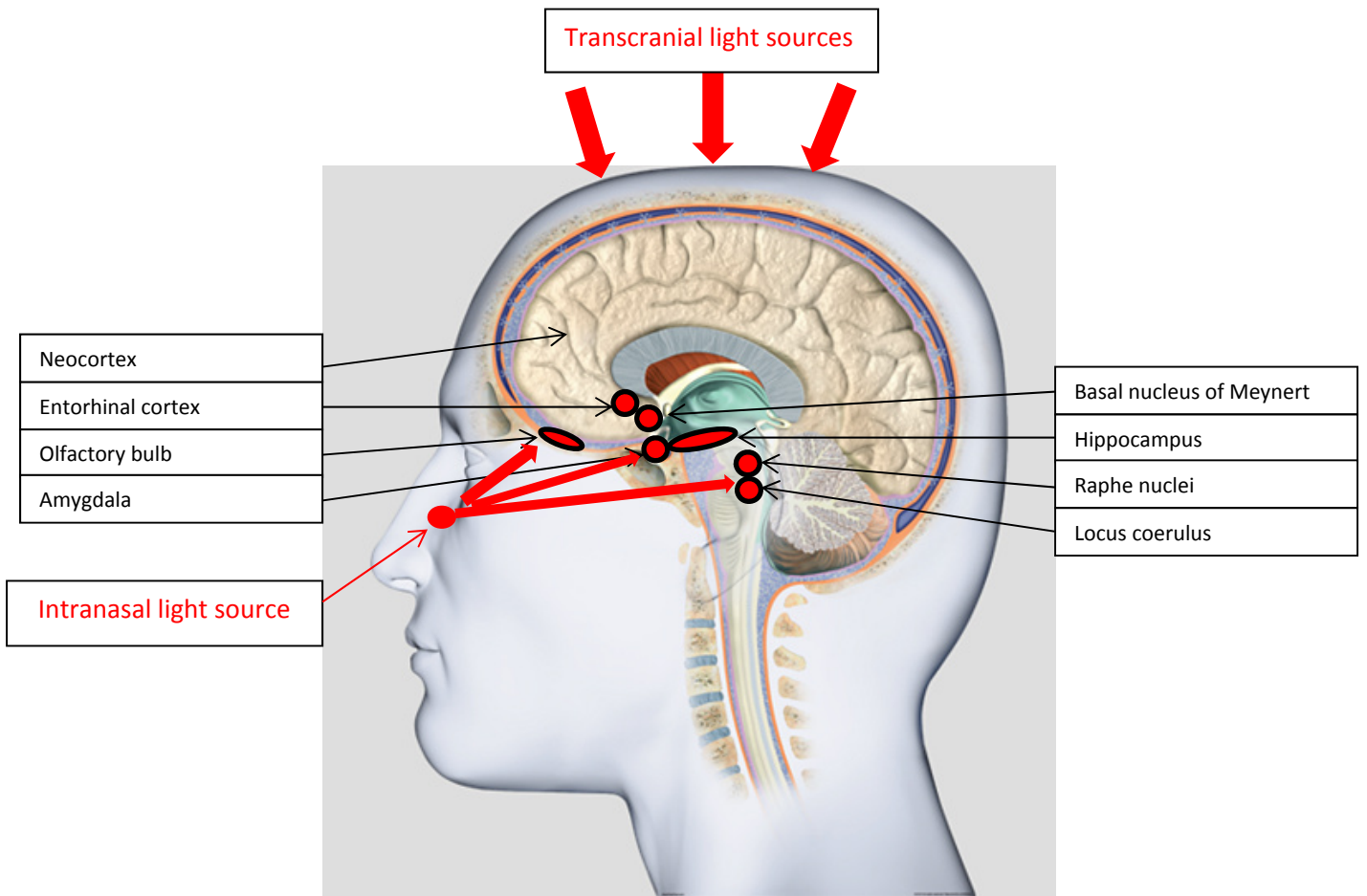
Much of the degeneration starts at the more primary regions of the brain particularly those that involve widespread projections, such as the nucleus basalis of Meynert which uses acetylcholine as neurotransmitters. Their degeneration leads into further degeneration in the neocortical regions in the late stage. The resulting cholinergic abnormalities are believed to contribute to cognitive deficits in aging and Alzheimer's Disease, non-cognitive behavioral abnormalities and deposition of toxic neuritic plaques.⁸ When the light energy is directed transcranially (from the outside of the skull), the grey and white matter will attenuate the energy before it can reach these deeper lying regions.

For this reason, light projected inside the nasal cavity would more easily reach the nucleus basalis of Mynert, raphe nuclei and the other nuclei, as represented in Figure 6.

The symptoms of early and intermediate stages of Alzheimer's disease can be identified with the degeneration of the neurons of these deeper regions, mostly in the lower (or ventral) sections of the brain:

- slight memory loss, especially short-term memory, but progressing to more significant loss;
- decrease in initiative and general motivation;
- depression;
- increasingly poor judgement and the misfiring of higher-order functions;
- mood disturbances, progressing to "sundowning" as discussed earlier.

Figure 6: Reaching regions of neuron losses from transcranial and intranasal light sources



Source of graphic: bodypartchart.com. Accessed August 22, 2013.
<http://www.bodypartchart.com/product/brain-cross-section/brain-cross-section-bpc-medium-image>

Although there are some bone structures between the light source in the nasal cavity and the key regions of potential neural loss in Alzheimer’s patients, these bone barriers are thin. In any event, the bones of the skull may not act as a barrier - it has been found that these bones curiously act as a channel to enable light energy to enter into the brain more easily.⁹ This allows light energy from a transcranial source to reach the top layer of the neocortex and that from the intranasal method to reach the lower parts of the brain.

For the light source in the nasal cavity, it is a shorter route to the targeted neurons in the lower regions in the brain with little barriers in between; making it a more efficient way to reach these targets.

From Figures 4a and 4b, it is apparent that the neocortical regions exhibit the greatest physical atrophy in late-stage Alzheimer’s patients. The symptoms of late-stage Alzheimer’s disease include:

- severe memory loss, including long-term memory;
- loss of the sense of an “autobiography” due to the loss of the memory bank;
- severe language difficulty;
- paranoia and low control of basic instincts –manifested because of the higher-order neocortical regions’ inability to manage the primal regions.

The mechanism of action behind photobiomodulation to diminish apoptosis is yet to be fully understood. However, there is growing acceptance that systemic photobiomodulation stimulates the whole body to restore homeostasis by modulating dysfunctions in the systems.¹⁰ It could be another factor that adds to its effect on containing Alzheimer’s disease.

Determining the parameters

Wavelength

The above investigations suggest that if one irradiates Alzheimer’s disease brain cells with low level lasers in the red electromagnetic spectrum, he can improve the conditions of an Alzheimer’s disease patient. However, other facts support an improved set of parameters based on NIR for better results.

It is a fact that the longer the wavelength, the deeper the travel/penetration into the tissues, and the lower the energy required to do this. This advantage of more tissue coverage draws greater cellular response. When tested on rats, photons between 630 nm and 800 nm have been shown to penetrate up to 28 mm even in layers of tissues with relatively low transparencies such as skin, connective tissue, muscle, bone, and spinal cord (even though much is already dissipated after the initial 1 mm) with about 6% of the total energy density being detectable at the ventral surface.¹¹ Deeper tissue penetration with NIR obviously offers a better head start.

The depth of light travelling through tissues depends not only on the wavelength but also on the optical properties of the target tissue. The work of Abdo A et al suggests that the maximal penetration of light in the gray and white matter of the brain occurs at wavelengths at the NIR spectrum.¹²

A study also showed that transcranial light therapy using a 808 nm laser diode attenuated amyloid plaque development in the transgenic mouse model, implying the possible efficacy of this therapeutic method at around this wavelength for the all-important Alzheimer’s disease in humans.¹³

Pulsed frequency

Generally, under certain conditions, ultra-short pulses can penetrate deeper into the tissues than continuous wave (CW) irradiation. Pushing greater power to a pulsed light source delivers more energy, which can activate more cellular energy (ATP), as demonstrated in a study on rabbits.¹⁴ Under pulsed mode, the effective dosage is higher than the conventional calculation due the deeper travel into the

tissues. The other mechanism of action involves the first part of a pulse containing photons to take all chromophore molecules in the upper tissue layer to excited states, opening the way for more photons into the tissue during the next pulse. Using 808 nm lasers on rabbits, researchers demonstrated that pulsed lasers at 100 Hz and 1000 Hz produced superior results to continuous wave.¹⁵

Later researchers testing with 810 nm laser, found that pulsing at 10 Hz produced even greater recovery from traumatic brain injury than 100 Hz. They suggested that the antidepressant activity of the light therapy was a contributing factor.¹⁶

Summary of parameters

In summary, based on the large body of successful outcomes, the preferred set of parameters consists of a 810 nm LED light source, pulsing at 10 Hz with 50% duty cycle. Treatment time can be for 25 minutes, with the power intensity set at 10 mW/cm². This results in the light rays from the LED light source to be delivered over a wide area.

With these parameters, the dosage per treatment is conventionally calculated at 7.5 J/cm² post-duty cycle (10/1000W X 25 X 60 seconds X 50%). These parameters bring together what have been previously discovered to be most effective for brain stimulation when irradiating the brain through the nasal cavity.

Proposed protocol

Based on the understanding of the above, the proposed protocol for the application of intranasal light therapy may be divided into three sections: 1. Prevention, 2. Early and Intermediate Stage, and 3. Advanced Stage. Intranasal light therapy with the parameters described above is central to the recommendations here.

1. Prevention

With the knowledge that any cell with mitochondria (including neurons) when subjected to photobiomodulation can be stimulated into a homeostatic recovery process, regular light therapy is recommended for anyone. After more than 45 years of data, no major side effects have been identified with low level light therapy.¹⁷

As a general rule, after the age of 45, degeneration becomes more apparent, although conditions vary between people, depending on genetics and lifestyle. One of these could be the slowing down of memory and cognitive ability. As discussed earlier, in the early stages of Alzheimer's disease, these are largely associated with the primary regions of the brain that are accessible to light energy from the nasal cavity.

The onset of Alzheimer's disease is unpredictable. However, the number of people afflicted with this disease is growing. Therefore it could be life-saving to take any convenient measure to minimize the risk of succumbing to this disease. One method that could be effective to help prevent this disease would be

the regular use of intranasal light therapy. Even if the user is not at risk for Alzheimer's disease, the other benefits that are derived from the regular use of the therapy, especially after 45 years old, would make this therapy to a key component of one's lifestyle. Using it at least 2 to 3 times a week would be recommended to prevent the onset of dementia and Alzheimer's disease.

2. Early to Intermediate Stage

Deteriorating memory and irrational behavior are signs of the neurons starting to degenerate. This calls for repair to the neurons in these affected regions, and to more aggressively slow down the degenerative process.

For this stage, it is recommended that intranasal light therapy be applied at least once a day, preferably twice - once in the morning and once in the evening (with at least 6 hours in between to prevent the risk of over-stimulation¹⁸).

3. Advanced Stage

In the advanced stage, the all-round loss of neurons is significant, which will be massive in the neocortex. Intranasal light therapy may not reach much of these areas, although some of the effect may get through from systemic distribution associated with photobiostimulation.^{17 19} At this stage we want to cover the brain comprehensively.

The use of transcranial light therapy, which introduces light from outside of the skull, directed to the neocortex, coupled with intranasal light therapy could give us this thorough coverage. This combination offers a new dimension to treating advanced stage Alzheimer's disease.

Conclusion

The debilitating effect of Alzheimer's disease is punishing an increasing number of families. There are many concurrent research being carried out to find an effective treatment. To date, none that is widely accepted as safe and effective exists. Based on the science and related evidence, intranasal light therapy has the potential to be the low cost, convenient and effective proposition. For the advanced stage, the transcranial light therapy should be introduced into the equation.

Much of the observations in this report have been based on available scientific understanding and anecdotal feedback. It awaits controlled studies to validate the largely anecdotal data. The devices are already in use in the field for a variety of conditions. Safety has never been a major issue with photobiomodulation modalities such as this. With the growing popular use of this technology, anecdotal data continue to build up.

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