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 that deaths are increasing. It is extremely debilitating to the families, and its vast economic cost urgently calls for an effective treatment. Yet, none todate has been found to be effective.

Intranasal light therapy, which is biophysical approach, offers a 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 now 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 respond positively to an exposure of low intensity light in the red to near infrared red 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 should see a similar positive response.

Many of the key regions of the brain that suffer degeneration and contribute to the onset of Alzheimer's disease are located in the underside and middle part of the brain. This is especially so for the early onset of the disease. They are most easily accessible from the nasal cavity, requiring less power than if directed from the outside of the skull. This also allows a low cost and highly convenient device to be developed, which results in this proposal for intranasal light therapy devices to treat this disease.

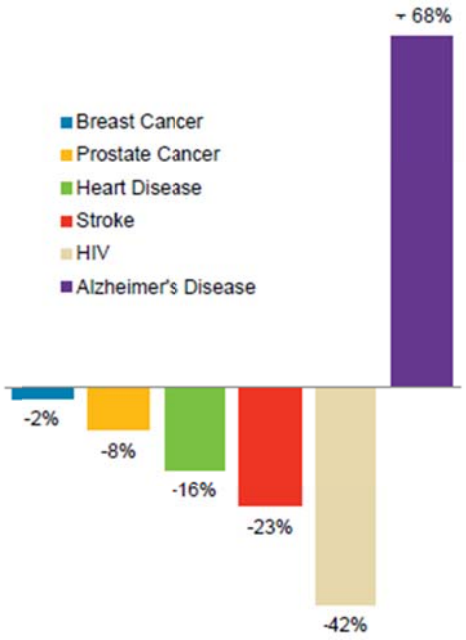
Based on literature and observable results, the optimum offering is a low intensity light in the 810 nm wavelength pulsing at 10 Hz. Energy in the region of 10 -15 mW/cm² delivered over 25 to 30 minutes, would be desirable to deliver the necessary dosage. Early cases of human use are very encouraging with consistent reports of significant improvements in the conditions of Alzeimer's disease with no observed adverse effects. Instead, the subjects report other improvements that indicate systemic healing in the body that are already reported in scientific literature for visible red intranasal light therapy.

Based on an understanding of the scientific bases, various protocols can be recommended. For advanced stage where there is massive degeneration in the neocortex regions, a combination with the transcranial method could have added therapeutic effects.

Introduction

Alzheimer's disease and to a lesser extent dementia, could be one of the most worrying diseases of this century. Modern medicine has contributed to the reversal in the growth of breast cancer, prostate cancer, heart disease, stroke and HIV. As the population lives longer, there is no let-up in the growth of Alzheimer's disease cases, which has grown significantly. Worse still, it is a burden for the whole family. See Figure 1 below.

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



Source: Alzheimer's Association

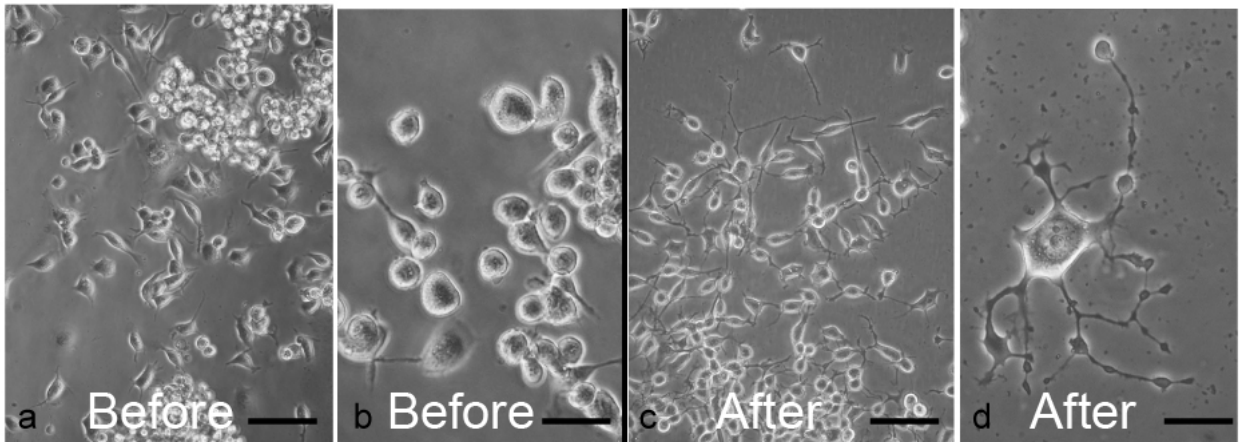
Data shows Alzheimer's disease to be the only cause of death among the top 10 in America without a way to prevent it, cure it or even slow its progression. Deaths from Alzheimer's disease increased 68 percent between 2000 and 2010, while deaths from other major diseases, including the number one cause of death (heart disease), have decreased.[1]

Alzheimer's disease in its advanced state has been identified with shrunken brains – the result of neuron loss and neurodegeneration. There may be various causes for the disease but the common result is that the disease results in the death of brain cells or neurons. If we could introduce an intervention that counters or slows this degenerative process, we may have a viable therapy for Alzheimer's disease. Herein is the potential of low intensity light therapy for this purpose, often termed as *photobiomodulation*.

Cell repair and regeneration with photobiomodulaton

The years of research reveal that low energy light in the visible red and near infrared red (NIR) stimulate cellular activity which activates a healing process. These include wound healing,[2] skin rejuvenation,[3] and in sports medicine for musculo-skeletal injuries and related pain.[4] When observed at cellular level, researchers found that cells repair themselves when exposed to photobiomodulation, even neurons, that previously had their neurites (composed of dendrites and axons) shortened from oxidative stress, would have the neurites re-elongated.[5] See Figure 2.

Figure 2: Neurite Elongation Experiment



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

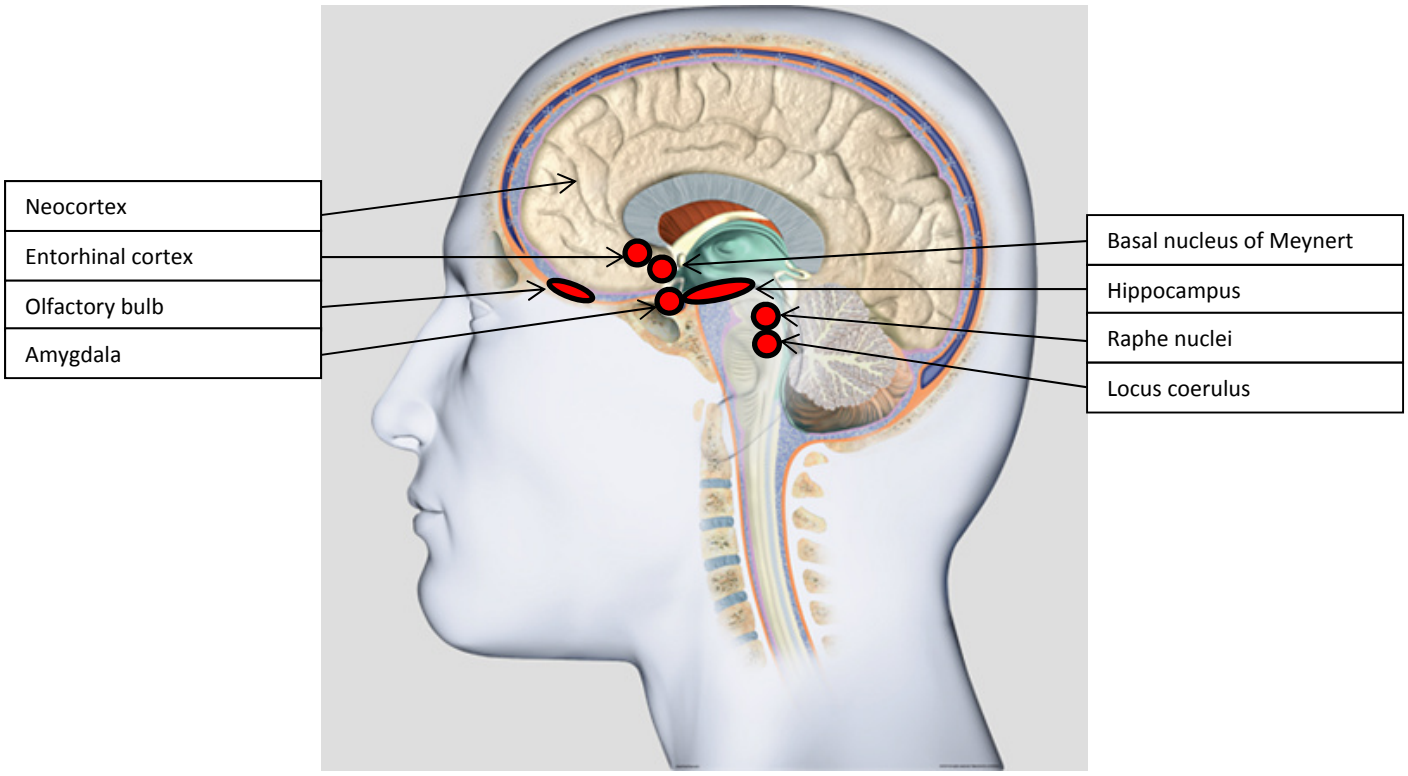
This points to a viable basis to support a proposal for light energy with similar characteristics to irradiate the neurons in the brain of an Alzheimer's disease patient to attempt to arrest the progression or even reverse the disease. The neurons of these patients undergo a similar loss of neurites before they progress to full apoptosis. So, subjecting these cells with neurobiostimulation can also 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 red or NIR light energy.

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.
http://www.bodypartchart.com/product/brain-cross-section/brain-cross-section-bpc-medium-image

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

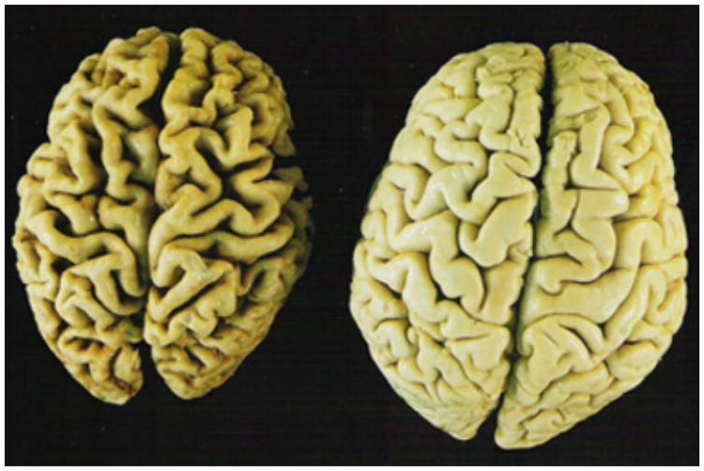
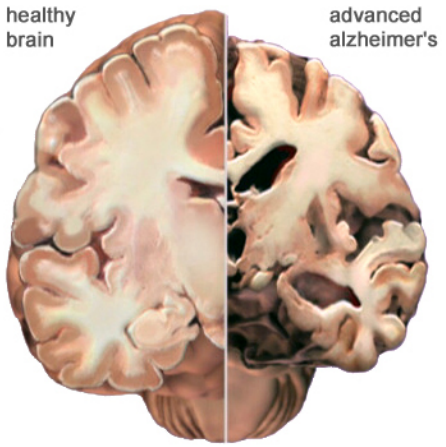
- *Neocortex.* These are the areas of higher order association. Advanced stage Alzheimer's disease is identified by massive loss in this region, resulting in the loss of the "person".
- *Entorhinal cortex* and *hippocampus*. Memory is dependent on the health of these areas covering episodic and autobiographical 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*. It is a small nucleus that supports the cortex with independent widespread cholinergic projections, using 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*. It is a small nucleus in the pons utilizing norepinephrine as a neurotransmitter. This also has independent widespread projections in the cortex. It 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*. They are groups of neurons 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 acecoline, a neurotransmitter involved in the pathology of Alzheimer's disease and treatment. The disease may also be caused by a pathogen entering the brain via olfactory pathways caused by a dysfunctional olfactory bulb.

In the midst of potential massive neuron loss, most of the primary areas in the brain are essentially intact until the end stage of the disease. Hence the patient's body carries out life-sustaining functions with significantly diminished control of voluntary thoughts and memory.

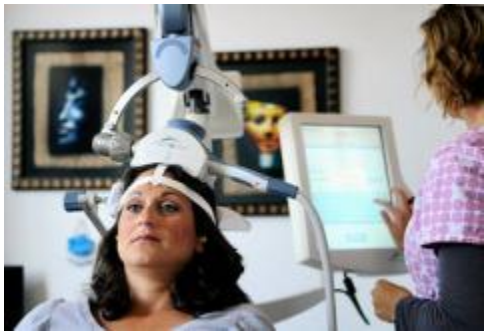
Since it forms most of the human brain, degeneration in the neocortex, or cortical atrophy, is most obvious in an autopsy of an advanced Alzheimer's disease patient. Massive neuron loss in this widespread region results in higher order functions supported by the frontal, parietal and temporal lobes. However, by the time we witness this event, the other regions identified above would have also suffered massive loss. See Figure 4a and 4b.

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

Figure 4a: Top view comparison	Figure 4b: Cross-section comparison
	

Since we already know that cells that are subjected to photobiomodulation can heal, we would expect the affected parts of the brain to heal. The question is how can we do this? Up to now, transcranial light therapy has been offered as a possible effective method of photobiomodulation to help 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 that are located closest to the light source. Recent research, mainly based on laboratory mice studies, 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 brain of a human being is much larger than that of a laboratory mouse by many orders of magnitude. So the effect of a transcranial with the same parameters, particularly related to intensity and dosage, 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 tissue barrier, and greater proximity between the light source and the targeted areas of degeneration.

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.

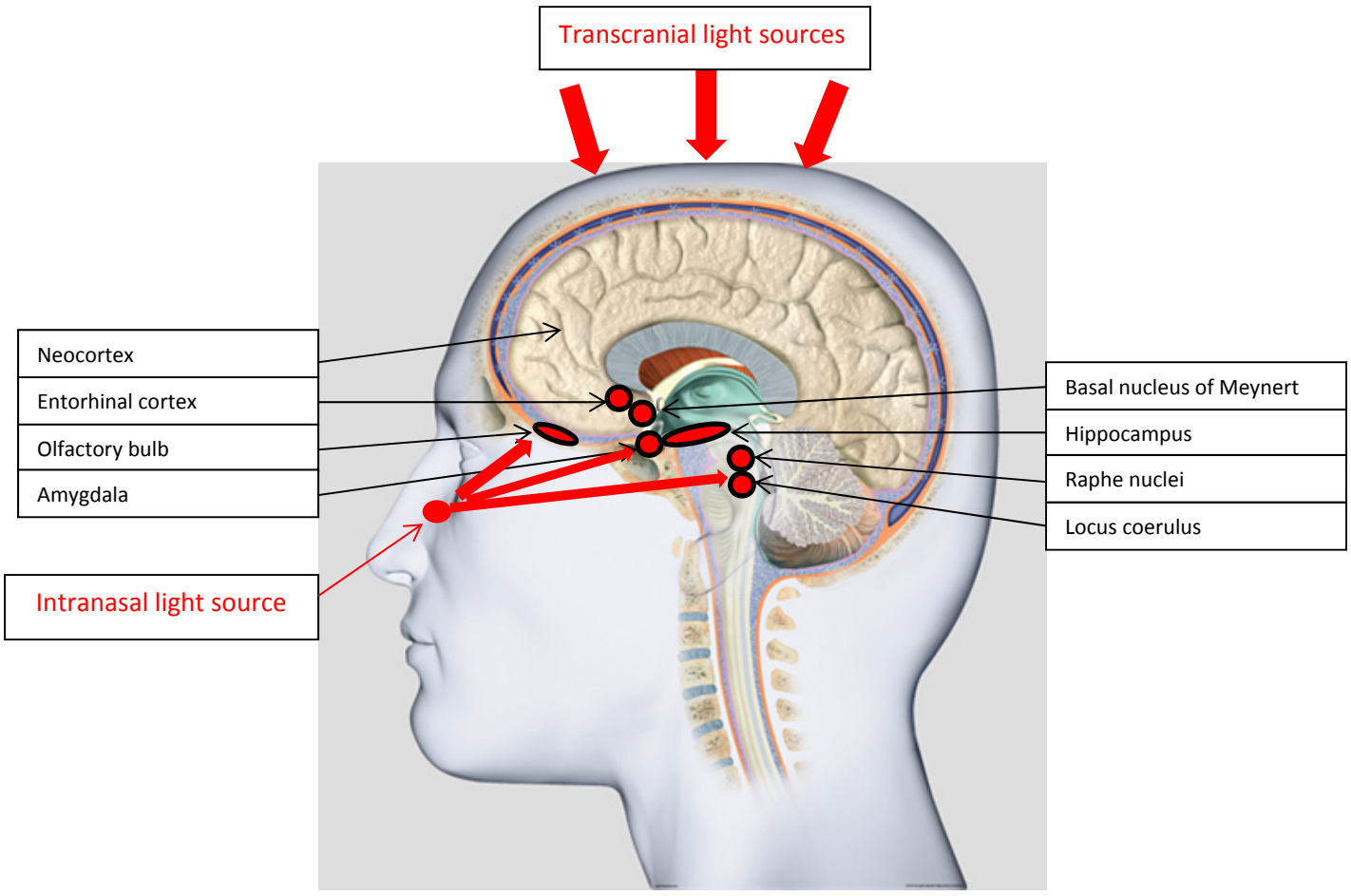
Much of the degeneration starts with the more primary regions of the brain particularly those that involve widespread projections, such as the nucleus basalis of Meynert. Their degeneration also leads to further degeneration in the late stage. It is widely believed that cholinergic abnormalities contribute to cognitive abnormalities in aging and Alzheimer's Disease, non-cognitive behavioral abnormalities and deposition of toxic neuritic plaques. [8] When directed transcranially, the materials in grey and white matter will likely absorb the photons before they can reach these deeper lying regions.

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 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" – which is identified by anxiety, fear, agitation and hallucinations.

For this reason, a light source that originates in the nasal cavity would be more efficient in reaching the nucleus basalis of Mynert and the other sources of neurotransmitters. This is visually represented in Figure 6.

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

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. However the bone barriers are thin and it has been found that bone in the skull may surprisingly act as a channel, not a barrier for light to penetrate into the brain.[9] This helps the transcranial method to reach the top layer of the neocortex and the intranasal method to reach the lower parts of the beain,A shorter route from the light source to the targeted neurons in the lower regions in the brain would result in lower loss of light energy, making it a more efficient way to reach the various targets in the lower regions of the brain.

Evidence of intranasal light therapy on Alzheimer's

Melatonin secretion decreases in Alzheimer´s disease. Researchers have postulated tthat its decrease to be responsible for the circadian disorganization, decrease in sleep efficiency and impaired cognitive function. This has been identified as "sundowning" as discussed earlier.[10] In 2002, 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, score in mini-mental state exam (and score in Wechsler memory scale for adult (WMS) increased in the Alzheiner's disease group, but there was no significant change for the gastric ulcer group.[11]

Alzheimer's disease is associated with widespread deposits of amyloid ß plaques in the brain, suggesting that these proteins induce neurodegeneration associated with the disease.[12] Since Alzheimer's disease closely identifies with neuronal apoptosis, a group of researchers experimented to see if subjecting neurons to light therapy would inhibit this degenerative process. They induced apoptosis on the brain cells of rats with an amyloid ß protein, and then irradiate the neurons with LED of 640 nm wavelength at 0.09 mW/cm² for 60 minutes. The therapy diminished the apoptosis significantly.[13] In a further experiment, they found that the same cells secreted anti-apoptosis factors, and promoted further neuronal viability.[14]

The mechanism of action behind photobiomodulation to diminish apoptosis is yet to be fully understood. However, there is an increasing acceptance that systemic photobiomodulation stimulates the whole body to restore homeostasis by modulating dysfunction in the systems.[15] It could be another factor that adds to its effect on countering Alzheimer's disease.

Determining the parameters

<u>Wavelength</u>

The above investigations suggest that if one irradiates Alzheimer's disease brain cells with red light or low intensity lasers, he can improve the condition of an Alzheimer's disease patient. Scientific 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. Researchers recognise that it is this range of wavelengths that draw the greatest cellular response as opposed to the need to have this wavelength merely for tissue penetration. 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.[16] Deeper tissue penetration obviously offers a better head start, and hence the longer NIR should be considered.

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.[17]

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.[18]

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.[19] 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. Using 808 nm lasers on rabbits, researchers demonstrated that pulsed lasers at 100 Hz and 1000 Hz produced superior results to continuous wave.[20]

Later researchers testing 810 nm laser found that pulsing at 10 Hz found that this 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.[21]

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: Prevention, Early and Intermediate Stage, and 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) that is 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.[22]

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 Alzhemier'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 does is not a 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 intranasal light therapy.

2. Early to Intermediate Stage

If the patient already has signs of Alzheimer's disease, such as deteriorating memory and irrational behavior, it suggests that the neurons have begun 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, once in the morning and once in the evening (with at least 6 hours in between to prevent the risk of over-stimulation[23]). Based on feedback, many users enjoy the experience of the health benefits from the therapy, to the extent that they gladly apply it more than once daily.

3. Advanced Stage

In the advanced stage, the all-round loss of neurons is significant, much of 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.[22] [24] At this stage we want more comprehensive coverage of the brain, covering as much real estate as possible

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 pockets of concurrent research on finding an effective treatment. Todate, 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 a low cost, convenient and effective proposition. This is supported by increasing number successful case studies.

Much of the observations in this report have been based on available scientific understanding and anecdotal feedback. Rigorous clinical investigations are highly desirable to confirm the effectiveness of this potentially important offering.

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