White Paper WP0901

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The Development of Phototherapy for Parkinson's Disease

Phototherapy is the treatment of a disease or disorder with specific wavelengths and intensities of light that cause a beneficial biochemical change. For example, special wavelengths of light are used to treat multiple sclerosis, acne, psoriasis, eczema, vitiligo and jaundice.[1,2,3,4] Light is the most efficient way of producing and assimilating vitamin D_3 for calcium and phosphorus absorption in the body.[5]

For hundreds of years, light was the only effective treatment for tuberculosis.

Near the turn of the 20th century, Florence Nightingale discovered that patients healed more rapidly when exposed to sunlight, and she was instrumental in hospitals redesigning their patient wards to allow maximum natural light exposure.[6]

Florence Nightingale pioneered the use of light for healing patients.

Light and the Brain

It should come as no surprise that light also elicits beneficial responses in the eyes and brain. Circadian rhythms are regulated by light, which in turn helps regulate the neuroendocrine system.[7] For example, serotonin, adrenalin cortisol and dopamine are activated by light. Other neuromodulators such as melatonin are suppressed by light and are activated by darkness.

Light Recommended as First-Line Treatment

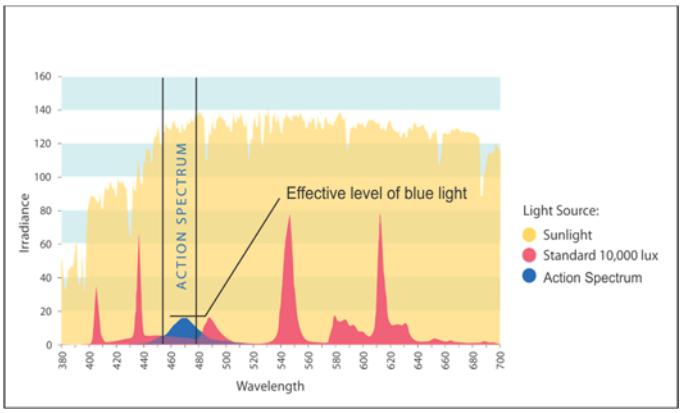
In 1984, the first application of light therapy for seasonal depression was published by the National Institutes of Health.[8] Over the past 30 years therapeutic light has been investigated for other major depressive disorders, bipolar disorder, sleep disorders, shift-work sleep disturbances, and jet lag.[9] Light Therapy is recommended by the American Medical Association, the American Psychiatric Association, and the American Academy of Sleep Medicine as a first-line treatment for certain sleep and mood disorders.[10,11]

The first applications of light therapy for mood and sleep disorders used bright polychromatic, fluorescent light. The most effective intensity of light was eventually found to be 10,000 lux. As a comparison, indoor light is approximately 50 – 200 lux, while sunlight can be as bright as 100,000 lux.

Action Spectrum of Light

In 2001 a major discovery changed our understanding and application of light therapy. Researchers found that a specific bandwidth of light was primarily responsible for the circadian and alerting response. This bandwidth is called the Action Spectrum, and its peak bandwidth is 470 – 480 nm.[12]

This discovery meant that specific bandwidths of light were more effective than others, and could yield



effective results at a fraction of the intensity of bright light therapy. Low-intensity light therapy may be critical for Parkinson's sufferers, because photosensitivity is associated with Parkinson's disease.[13]

Light in Parkinson's Disease

Light therapy research in Parkinson's may have first been used to study sleep problems.[14,15] Parkinson's patients appear to have a circadian related problem with sleep, in that they tire early in the day and waken too early at night.[16] This may indicate that their circadian and melatonin rhythms are cycling too early in the day. Some evidence supports this theory.[17,18,19] REM sleep behavior disorder (RSD) is also associated with Parkinson's.[20] RSD may be circadian related, and preliminary studies using melatonin in RSD show improvement.[21,22] Interestingly, Parkinson's studies investigating light therapy for sleep also found improvement in motor symptoms. This

discovery led to further investigations with light for motor symptoms in Parkinson's disease.

To date, five studies have been done with light therapy and Parkinson's.[14,15,23,24,25] The largest of these studies was a long-term retrospective analysis of 129 subjects, where the binned data averaged nearly four years.[24] During this several year study, investigators noticed a differential response depending on the spectral properties of the light therapy devices used. Patients responded better to certain light boxes and not as well to others. When checked, the spectral properties of these light boxes varied greatly. Thus the authors cautioned against the ad hoc use of available light therapy for Parkinson's disease.

This observation led to a number of unpublished pilot studies to determine a more optimal light device for Parkinson's.[26,27] These studies utilized various wavelengths of light (including 500 – 560 nm, 520 – 570 nm, 575 – 650 nm, etc.) and suggest that different wavelengths have different effects upon the therapeutic response. These studies showed that Parkinson's patients may respond better to action spectra similar to the action spectrum response for circadian regulation. However, it became apparent that more than one specific bandwidth of light was essential for Parkinson's, and thus the resulting color is different than the action spectrum for circadian regulation.*

Negative Effects of Long-wavelength Light

Additional unpublished data suggests that long-wavelength light may cause negative effects in Parkinson's disease. A pilot study used a crossover design to determine the effect of specific bandwidths of light, including red light. All of the patients on red light (575 – 650 nm) responded negatively and needed to be withdrawn from the study. Because of this negative response, it was determined that red light should be eliminated as much as possible. Because all commercially available bright light devices included substantial amounts of this long-wavelength light, it was determined that a specific bandwidth light device be designed which enhanced certain wavelengths, but reduced or eliminated the red spectrum.

Spectramax™ Specific Bandwidth Phototherapy

As a result of these pilot studies, Spectramax™ was developed to capture the effective spectra of light while eliminating the red. The intensities found effective in prior studies were applied to Spectramax™, and the overall intensity is approximately 1/10th that of traditional bright light therapy (~1000 lux or 250 – 500 µW/cm^2/sec). This level of irradiance is comparable with the low-intensity light therapy devices that have been found effective for Seasonal Affective Disorder, and the lower intensity should result in a more favorable tolerance of the phototherapy device and a reduction in adverse side effects. In an unpublished pilot study over 6 months, patients treated with prototype Spectramax™ phototherapy specifications responded as well as or better than the polychromatic light condition.[27]

Conclusion

Work in phototherapy and Parkinson's disease reveals that light may be beneficial for both motor and non-motor symptoms. Bradykinesia, tremor, rigidity, sleep and depression have all shown significant improvement in both placebo controlled and long-term open label studies. No study to date has shown any negative results, and light therapy has been shown to be well tolerated.

It is apparent that as with other circadian and affective disorders, specific bandwidth light at lower intensities than 10,000 lux may be advised, especially considering the dark adapted state of Parkinson's patients. Thus specialized phototherapy for Parkinson's is advised, as opposed to conventional bright light therapy.

Several pilot studies along with unpublished data from a long-term retrospective analysis have helped to identify an optimal, low intensity phototherapy device that enhances specific bandwidths while avoiding the potentially problematic red spectrum. Light is non-invasive and has shown only benign side effects. The risk-benefit ratio demonstrated by the pre-clinical and clinical work that has been done is sufficient to warrant the longer term, double-blind study with Spectramax phototherapy. Results from this study should be available in 2016.

* The spectral bandwidths for Parkinson's have not yet been released due to ongoing double blind investigations and the need for the participants to remain blinded as to the type of light they are receiving.

References

[1] Otto LL. Light as medicine? UWM researchers explain how. *UWM News: Today@UWM*. October 17, 2013. http://www5.uwm.edu/news/2013/10/17/light-as-medicine-uwm-researchers-explain-how/ Accessed August 4, 2015.

[2] Frohman EM, Brannon K, Alexander S, Sims D, Phillips JT, O'Leary S, et al. Disease modifying agent related skin reactions in multiple sclerosis: prevention, assessment, and management. *Mult Scler*. 2004;10(3):302-307.

[3] Diffey BL. Ultraviolet radiation physics and the skin. *Phys Med Biol*. 1980;25(3):405–426.

[4] Titus S, Hodge J. Diagnosis and treatment of acne. *Am Fam Physician*. 2012;86(8):734-740.

[5] Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266-281.

[6] Nightingale F. Notes on nursing: what it is, and what it is not. New York, NY: Cambridge University Press; 2010 [first published, 1898].

[7] Cajochen C. Alerting Effects of Light. *Sleep Med Rev*. 2007;11(6):453-464.

[8] Rosenthal NE, Sack DA, Gillin LC, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*. 1984;41(1):72-80.

[9] Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med*. 2005;35(7):939-944.

[10] Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162(4):656-662.

[11] Morgenthaler T, Lee-Chiong T, Alessi C, et al. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. An American Academy of Sleep Medicine Report. *Sleep*. 2007;30(11):1445-1459.

[12] Brainard GC, Hanifin JP, Greeson JM, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci*. 2001;21(16):6405-6412.

[13] Wink B, Harris J. A model of the Parkinsonian visual system: support for the dark adaptation hypothesis. *Vision Res*. 2000;40(14):1937-1946.

[14] Willis GL, Turner EJ. Primary and secondary features of Parkinson's disease improve with strategic exposure to bright light: a case series study. *Chronobiol Int*. 2007;24(3):521-537.

[15] Paus S, Schmitz-Hübsch T, Wüllner U, Vogel A, Klockgether T, Abele M. Bright light therapy in Parkinson's disease: a pilot study. *Mov Disord*. 2007;22(10):1495-1498.

[16] Willis GL. Parkinson's disease as a neuroendocrine disorder of circadian function: dopamine-melatonin imbalance and the visual system in the genesis and progression of the degenerative process. *Rev Neurosci*. 2008;19(4-5):245-316.

[17] Bordet R, Devos D, Brique S, et al. Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. *Clin Neuropharmacol*. 2003;26(2):65-72.

[18] Fertl E, Auff E, Doppelbauer A, Waldhauser F. Circadian secretion pattern of melatonin in de novo Parkinsonian patients: evidence for phase-shifting properties of l-dopa. *J Neural Transm Park Dis Dement Sect*. 1993;5(3):227-234.

[19] Fertl E, Auff E, Doppelbauer A, Waldhauser F. Circadian secretion pattern of melatonin in Parkinson's disease. *J Neural Transm Park Dis Dement Sect*. 1991;3(1):41-47.

[20] Arnulf I, Neutel D. Herlin B, et al. Sleepiness in Idiopathic REM Sleep Behavior Disorder and Parkinson Disease. *Sleep*. 2015;1:663-614.

[21] Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov Disord*. 1999;14(3):507–511.

[22] Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res*. 2010;19(4):591–596.

[23] Artemenko AR, Levin VI. Light therapy of patients with parkinsonism. *Zh Nevrol Psikhiatr Im S S Korsakova*. 1996;96(3):63-66.

[24] Willis GL, Moore C, Armstrong SM. A historical justification for and retrospective analysis of the systematic application of light therapy in Parkinson's disease. *Rev Neurosci*. 2012;23(2):199-226.

[25] Rios Romenets S, Creti L, Fichten C, et al. Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease -- a randomized study. *Parkinsonism Relat Disord*. 2013;19(7):670-675.

[26] PhotoPharmics Internal Report. Aug 2012;1-18.

[27] PhotoPharmics Internal Report. Sep 2012;1-24