Baylor Scott and White Research Institute

Assessing feasibility of prolonged repetitive near infrared light stimulation on cognitive and behavioural symptoms in early to mid-stage dementia

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Title: Assessing feasibility of prolonged repetitive near infrared light stimulation on cognitive and behavioural symptoms in early to mid-stage dementia

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1. Introduction/Background

Neurodegeneration and dementia are speculated to be related to pathologies of cerebral blood flow (CBF, Chaudharyet al.2013, Spilt et al., 2005). Another argument for a possible role of impaired blood flow in the etiology of dementia is that Alzheimer's patients with brain damage (regions of magnetic resonance imaging [MRI] signal hyperintensity) have increased oxygen extraction per mL/min. That is, blood supply rather than demand seems to be the problem. Oxygen extraction would be expected to be unaltered if reduced blood flow were secondary to tissue damage (Spilt et al., 2005; Yamaji et al., 1997). Single photon emission computed tomography (SPECT) studies have shown CBF to be significantly reduced in the frontal and temporal regions in fronto-temporal dementia (FTD) patients (Miller et al., 1997; Read et al., 1995). The anatomical distribution of reduced rCBF corresponds to the pattern of neuropsychological deficits (McMurtray et al., 2006). Not surprisingly, MRI and computed tomography (CT) in FTD patients shows atrophy in the frontal and temporal regions (Mendez et al., 1996; Neary & Snowden, 1996). Positron emission tomography (PET) imaging in FTD patients reveals reduced glucose metabolism in the frontal and anterior temporal lobes, and also in the cingulate gyrus, insula, uncus, and subcortical structures (Garraux et al., 1999; Ishi et al., 1998; Jeong et al., 2005). Grimmer et al. (2003) performed a longitudinal study on ten patients diagnosed with FTD. At the initial assessment, FTD patients had reduced metabolic activity compared to controls in frontal cortical areas, the caudate nuclei, and the thalami. On a 1-2 year follow-up, significant progression of the original deficits was observed in the orbitofrontal cortex and the subcortical structures. Therefore, a treatment mode that increases the cerebral blood flow should be beneficial for the patients with above mentioned disease entities.

It has been shown that infrared light stimulation increases cerebral blood flow (Uozumi et al 2010). In addition to that, Bradford et al have shown that infrared exposure increases cell

viability against UV exposure. Therefore, infrared exposure can be therapeutic in two modes. It can increase the cerebral blood flow preventing degeneration and also increase cell viability. A first pilot controlled double blind studies were conducted at Quietmind Foundation, Plymouth Meeting, PA (N=11) (Berman, 2012. PMID: 28593105) and at BSW Temple research facility (N=12) as a first pilot feasibility studies designed for 4 weeks treatment. Studies involved subjects diagnosed with early to mid-stage dementia where 8 subjects were treated with near infrared light stimulation (active devices) with two sessions per day six minutes each for 28 consecutive days, and 3 and 4 subjects (respectively) treated with identically looking placebo (inactive devices) for same duration of time. Two independent studies observed no reported adverse effects whatsoever in all eleven and twelve treated cases. There was mean improvement of Mini-Mental Status Exam score of +5 (out of 30) for the treated dementia subjects (ranging from 3 to 8 in increased scores).

A meta-analysis by Grove et al. (2000) found that for predicting outcomes in human health or behavior, statistical or mechanical methods of interpreting data consistently equaled or outperformed “clinical judgment.” The results of Grove et al. are consistent with many studies showing that diagnostic labels do not add incremental predictive or prognostic validity above and beyond the symptoms from which they are inferred. Thus, the purpose of this study is to investigate the feasibility of near infrared stimulation for improving cognitive, behavioral, and memory functions resulting from a dementing illness. We are primarily interested in the potential of near infrared phototherapy to recruit what plasticity remains in the brain, not to remediate the specific disease etiology which, even with the best diagnosis, is often or usually unknown. Given the substantial evidence linking dementia to reduced regional CBF and the cytoprotective and neuronal rehabilitative features of near infrared light stimulation (Uozumi et al 2010, Bradfordt et al.,2005), we hypothesize that repeated exposure to near infrared stimulation will increase cerebral blood oxygenation, increase cell viability resulting in improvement of subjects’ cognitive and behavioral deficits.

2. Significance

There is no treatment currently available that offers an effective substantive slowing or reversal of dementia-related symptoms including behavioural dysregulation, memory deficits, and executive functions. Research suggests that impaired regional cerebral blood flow (rCBF) plays an important role in dementia. While a number of studies show that regulation of rCBF can be trained with biofeedback, no research has been published related to the application of infrared

phototherapy on the regulation of CBF. This study is to assess the feasibility for conducting a clinical trial to fill the gap in this area.

3. Objectives & Specific Aims

This study seeks to assess the ability to conduct a trial involving the delivery of brief infrared phototherapy in patients with early to mid-stage dementia. This study will assess the feasibility, recruitment of patients, adherence to usage, cognitive improvement, immunological response and potential side effects, if such.

4. Methodology

4.1. Study Design

This is a randomized, double-blind, placebo-controlled trial using an active and sham version of the device. Random assignment using computerized random number generator. Patients will be randomized 2:1 ratio to receive either the active device or the sham matched device. The Office of Biostatistics will provide a set of randomized sealed envelopes for investigator. When a patient is recruited and consented, the coordinator dispensing the device (not the PI) will open the envelope and recorded on a list not available to the investigators or the people conducting any assessments. EACH helmet will be delivered with a highly visible tag with either an 'A' or 'B' respective to the study group the patient was randomized to. Study coordinator will know which device is the active or the sham unit. This information will not be available to the PI or sub-investigators that will carry out the study. They will operate identically to all external observation since infrared light is invisible.

First pilot feasibility study (N=12) performed at BSW facility designed for 4 weeks treatment was based on earlier published pilot study (N=11) done at Quietmind Foundation, Plymouth Meeting, PA (Berman, 2012. PMID: 28593105). Aforementioned pilot study with 4 weeks of consecutive treatment and 12 enrolled subjects was successfully completed at BSW Health research facility in Temple, TX and proved to be safe and effective by accomplishing all projected goals. In this study subjects will receive 8 consecutive weeks of treatment with identical devices twice a day / everyday, as it was used in previously successful study done by our group. This is to be considered an extended treatment feasibility study. The devices proposed to be used in this study have identical technical characteristics to devices which were successfully used in previous BSW pilot study.

Marvin H. Berman PhD, the President of Quietmind Foundation and PI for the original pilot

clinical trial with the NIR helmet with dementia patients will direct the trial activities for 50 subjects at the Quietmind Foundation clinic in Elkins Park, PA and will available for consultation to the PI and sub-investigators of this study. The study coordinator of BSW will hold the device blinding information, i.e., active and sham (Helmet A or B).

4.2. Subject Selection/Participants

This is a feasibility study to assess patient compliance, recruitment, safety and potential cognitive and behavioural performance improvement. With these goals in mind, this study aims to recruit 60 evaluable patients at BSW to demonstrate a good practice and statistical power to show effectiveness of proposed study.

Inclusion Criteria

- Aged 50-85 years with an independently provided diagnosis of dementia, probable Alzheimer's type.
- Dementia symptoms not greater than early to mid-stage dementia
- Generally healthy as indicated by recent physical examination within the last 6 months
- If labs are available within the last 6 months, renal function, hepatic function, cardiac function should be normal

Exclusion Criteria

- Diagnosed actively growing intracranial pathology (tumors etc.)
- Misusing illegal substances or alcohol
- Previous history of stroke
- History of aggression or violence
- History of major psychiatric illness
- No underlying CNS pathology (confined to tumor, epilepsy only)

Subject recruitment and enrollment plan

Potential subjects will come primarily from the Baylor Scott & White Healthcare system. The study coordinator will consent subjects that are eligible for participation.

Compensation

Subjects will be compensated US $75 for each completed visit.

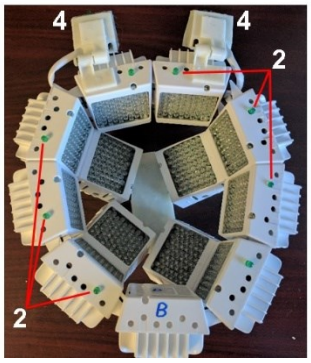
Subject Withdrawal

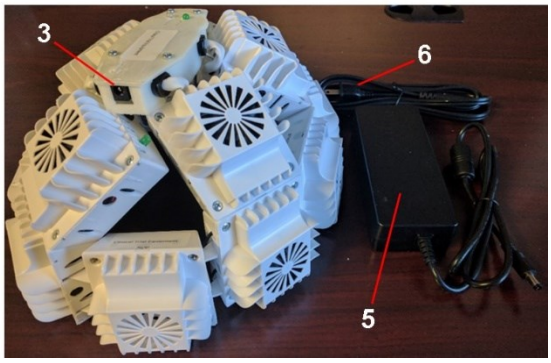
Subjects can elect to withdraw at any time, and investigators can terminate participation if they determine in their clinical judgment that the subject's mental status is incompatible with the minimum level of functioning acceptable for participation. Data collected up to withdrawal will be included in the analysis for comparative purposes.

4.3 Description of the study device

The portable device covers the head and weighs about 3.5 lb., and is made of light-weight, durable plastic, it is placed on the head with eye panels facing forward. Elastic straps holding the arrays together easily expand to conform to each subjects' head. Patients may notice slight warming of scalp after usage. This warming effect is similar to wearing a regular motorcycle helmet for a similar duration.

This helmet was successfully tested on first cohort of patients at BSW facility during first pilot feasibility/safety study and patients did not report any discomforts associated with usage of active or placebo devices. The treatment devices for this proposed study are custom designed and will be the same to previously used units.





1. "ON" switch
2. Green indicator light- illuminated when working correctly
3. 12 Volt DC power connector
4. Eye modules
5. 12 Volt power supply
6. Mains connector for the power supply

4.4 . Study procedures for individual visits/interventions and/or interactions

Near infrared light stimulation (1065-1075nm) exposure will be done for 6 minutes per session twice a day for duration of 8 weeks.

During each stimulation session, subjects will hear fans running and hear a start and stop tone that is emitted, but patients will not see infrared light. No discomfort or injuries will be expected from the use of the device. Helmet is lowered onto the subjects head from above and it will expand to accommodate and remain in contact. Placebo device control group patients will receive an identical device using sham infrared light therapy including visible operating lights and fan noises.

Randomization procedures

The Office of Biostatistics will provide a randomization schedule. When a patient is recruited and consented, the person dispensing the device (not the PI) will open the envelope and recorded on a list not available to the PI's or the people conducting any assessments. EACH helmet will have a highly visible tag with either an 'A' or 'B' on it and the coordinator administrating the use of the device are simply told to help with the device allocated in the randomization envelope. The helmets will operate identically to all external observation since infrared light is invisible.

Number of Visits, Visit Schedule, & Visit Procedures

	Visit 1				**Visit 2**				**Visit 3**
	Baseline	Wk 1	Wk 2	Wk 3	Week 4	Wk 5	Wk 6	Wk 7	Week 8
Q-EEG	X				X				X
Mini-Mental	X				X				X
Baseline ADAS-Cog	X								
Week 4 ADAS-Cog					X				
Week 8 ADAS-Cog									X
Case Notes	X				X				X
ECOG (caregiver)	X				X				X
FAQ (caregiver)	X				X				X
Historical Information	X								
Lawton ADL	X				X				X
BRIEF -A Informant Report (caregiver)	X				X				X
Training	X								
AE's		X	X	X	X	X	X	X	X
Compliance Testing					X				X
Telephone follow-up (weekly)		X	X	X		X	X	X	
Twice a day Helmet	X	X	X	X	X	X	X	X	X

Each subject will have their own helmet that they will take home in dedicated cushioned lockable case. Subjects will be required to make **3 visits (+/- 3 days)**. A 30 minutes Quantitative EEG analysis will be made to assess the power of delta (0-4hz), theta (4-7hz), Alpha (8-12hz), Beta (13-18hz) and high Beta (15-38hz) gamma waves before the device usage starts, mid-way through the study period (after 4 weeks) and at the conclusion of the study (8 weeks). In addition, the twice-a-day treatment sessions will be conducted at patient's home, one in the morning and one in the evening.

During the **first visit**, a base-line QEEG test, mini-Mental and Baseline ADAS-Cog testing will be conducted. Along with Case Notes, ECOG questionnaire (caregiver), Functional Activities Questionnaire (caregiver), Lawton ADL Questionnaire, BRIEF-A Informant Report (caregiver), and Historical Information Questionnaire will be conducted at this visit. The subject and the

caregiver will be then taught regarding the use of this device. A first device session will be conducted in the office. Then the subject will be allowed to take the device home for daily use. The subject will also be given a Home Study Diary to document what time they used the helmet each am and pm as well as a Daily Subjective Response Record to report what the subject did that day. The Home Study Diary and Daily Subjective Response Record will need to be completed each day while the subject is on the study.

The Coordinator will call the subject weekly, between visits, (or more frequent if indicated by evaluation during the initial visit) to check on the status/usage compliance subjects, AE's/SAE's, and also encourage them to call at any time with questions.

During **four-week visit** (mid-device administration point), the subject will undergo another QEEG test. Mini-Mental and Week 4 ADAS-Cog testing will be conducted. Along with Case Notes, ECOG questionnaire (caregiver), Functional Activities Questionnaire (caregiver), Lawton ADL Questionnaire, AE's and SAE's, and BRIEF-A Informant Report (caregiver) will be conducted at this visit. The subject will bring their study device with them at this visit. A meter within the device will be checked for compliance.

During **eight-week visit** (post-device administration point), the subject will undergo another QEEG test. Mini-Mental and Week 8 ADAS-Cog testing will be conducted. Along with Case Notes, ECOG questionnaire (caregiver), Functional Activities Questionnaire (caregiver), Lawton ADL Questionnaire, AE's and SAE's, and BRIEF-A Informant Report (caregiver) will be conducted at this visit. The subject will bring their study device with them at this visit. A meter within the device will be checked for compliance. The study device and its peripherals will be returned at this visit.

The first session will last approximately 180 min. It will include teaching the subjects to use the device (30 min) and testing (QEEG and dementia testing). The 4-week follow up section and the final session will take approximately 150 min each.

After the subject is consented the subject will be given a bar of soap and will be instructed to wash their hair prior to each scheduled visit to the clinic throughout the study. This approach has demonstrated to improve the quality of received signals and reliability of recorded QEEG. The improvement is due to the enhanced conduction from the clean surface of the skin, resulted

in better signal transmission from skin to QEEG gel and to the device.

4.5. Assessments and Data Manipulation

The Dementia Rating Scale (Appendix 1): Mini-mental and ADAS-Cog testing: allows the evaluator to examine attention, conceptualization (verbal and nonverbal), preservation (verbal and nonverbal), memory (verbal and nonverbal), and construction. The Functional Activities Questionnaire given to the caregiver is designed to assess what daily living areas are impacted by mental illness or disability. Lawton Activities of Daily Living Questionnaire is most useful for identifying how a person is presently functioning and to identify improvement and deterioration. Case notes will be completed by the subject including treatment starting and stopping times, compliance testing, behavioural observations, current mood, pain, and fatigue levels as well as sleep and appetite information. ECOG Questionnaire given to the caregiver can help clinicians to diagnose cognitive impairment more effectively and to better understand the limits, care needs and interventions appropriate to individuals. Brief-A Informant Report given to the caregiver was developed to assess the everyday behavioural manifestations of adults' executive control functions. Historical Information Questionnaire collects general information, medical history, education and Occupational history/current interests. Subjects will be queried about adverse events and serious adverse events at least at midpoint and post testing interviews.

Quantitative EEG (QEEG): The system will record 19-channels of EEG activity using the 10-20 measurement standard. A specially designed bathing cap with imbedded electrodes will be placed on the subject's head. Ear clip electrodes are placed on their earlobes to provide reference readings for comparison to the scalp recordings. Assessments will be performed by qualified trained personnel.

All tests are done face to face during Baseline, Week 4, and Week 8.

Data collection variables

Measurements include baseline, intermediate, and endpoints. After infrared light stimulation sessions single QEEG recordings, dementia rating score assessment will be made available during each session.

QEEG analysis using Neuroguide software (Thatcher, 2005) will provide comparative data of

each subject's EEG activity compared to established norms for age, gender, and handedness. The Dementia Rating Score, including Mini-mental and Baseline, Week 4 and Week 8 ADAS-Cog, Functional Activities Questionnaire, Lawton Activities Questionnaire, Case Notes, ECOG Questionnaire, BRIEF-A Informant Report, Home Study Diary, Daily Subjective Response Record, Historical Information Questionnaire, adverse events, serious adverse events and helmet readings will provide additional data points.

Data Storage & Maintenance

QEEG recording during subject's encounters will be saved as electronic data, dementia scale assessment data, as well as all questionnaires will be transcribed from paper questionnaire to electronic data in excel data sheets. The data will be maintained and stored in a password protected computer with encryption and located in a secured office (only assessable to the PI, study coordinator and sub-investigators). Paper questionnaires will be kept in a locked office.

Data will be stored in a password protected spreadsheet with limited access to those listed as key study personnel.

Once the publications are made, all data will be archived for 6 years without patient identifiers.

Data/Material Sharing

Study data will be shared with our collaborators for purpose of writing scientific papers, after removing all PHI, and according to a signed agreement between Baylor Scott & White and Quietmind Foundation. Mean results (example: QEEG power) will be sent in graphical form without patient identifying criteria via secured mail.

Data Analysis

Report of variables at each time point will be done with means (standard deviation) or median (range), if appropriate, for continuous variables. Frequency and counts will be reported for categorical variables. Based on the results of this study a full scale study will be planned and preliminary results will be used for possible publication and grant submission.

4.6. Reporting adverse events or other significant events

There have been no adverse event reports from previous unpublished pilot study (N=12)

performed at BSW Health, Temple, TX and published pilot study (N=11) performed by Marvin Berman (Berman et al, 2012. PMID: 28593105). There are no adverse event reports in the peer-reviewed literature for near infrared light stimulation or of dementia subjects wearing helmet-like devices[2]. Subjects will be verbally queried at each session about the subject's response to the previous device usage to detect any adverse impacts, pre/post usage session data will be examined and significant alterations in physiological response, e.g., pain, dizziness, agitation will immediately be reported to the study coordinator and principal investigator who will assess the response and take appropriate action. All such events will be included in the daily subjective response record. Any and all adverse events encountered during the study will be reported to the IRB.

4.7. Human Subjects

Risks

Proven safety and minimum risk of harm for the human subjects; slight warming of scalp was reported in previously published and internal study. This effect is similar to wearing a motorcycle helmet for a short period of time (6 min twice a day). Physical: Neck strain due to weight of the helmet. This is addressed by using a lighter design, reducing study time.
Privacy: Minimum and necessary information will be taken with minimum interference to privacy.
Psychological: Isolation will be minimized by QEEG recording in a smaller room in the presence of the investigator or bystander who the patient is comfortable with, reduced recording time.

Benefits

This proposal is for a study to evaluate the practicality to carry out a full scale 8 weeks study. Based on previous pilot study (N=12) conducted at BSW Health with no expected benefits, we observed benefits for patients with active devices by improved cognitive function, executive performance, and received very positive feedback from family members (caregivers) regarding overall improvement in daily routine and quality of life of patients (improved mood, appetite and behaviour). Therefore, we assume similar changes and expect similar response and benefits from our patients and caregivers with this proposed study.

4.8. Safety Evaluation and Risk-Benefit Justification

Subjects will be monitored and evaluated during each visit, queried as to comfort and reactions

to device usage, along with weekly phone calls to check on patients. We also encourage and available for our patients to call with any concerns or questions.

5. Conflicts of Interest Disclosure(s)

No conflicts to be declared.

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7. Attachments/Appendices

The Dementia Rating Scale (Mini-Mental Exam and Baseline, Week 2 and Week 4 Adas-cog)

Functional Activities Questionnaire

Lawton Activities of Daily Living Questionnaire

Case Notes

ECOG Questionnaire

Brief-A Informant Report

Home Study Diary

Daily Subjective Response Record

Historical Information Questionnaire