Cover Page

PROTOCOL: A Feasibility Study of Adherence to Light Therapy for Maintenance Treatment of Major Depressive Disorder

Version 2.1, date: June 14, 2021.

NCT04944758

Note: This feasibility study was terminated early because we received funding for a larger, more rigorous feasibility trial. Only 1 participant was entered. No statistical analysis was conducted.

PROTOCOL: A Feasibility Study of Adherence to Light Therapy for Maintenance Treatment of Major Depressive Disorder

Principal Investigator: Raymond W. Lam, MD, r.lam@ubc.ca
Co-Investigators: Erin E. Michalak, PhD; Aiden Scott; André Do, MD; Victor Li, MD, PhD; Edwin M. Tam, MDCM; Jill K. Murphy, PhD.
Version 2.1, Jun-14-2021.

Background

According to Canadian statistics, at any given time at least 1 in 20 people (5% of the general population) are suffering from clinical depression (i.e., major depressive disorder or MDD), with a lifetime prevalence estimated at 14% (Palay et al, 2014). MDD is associated with significant quality of life (QoL) impairment and societal burden; the World Health Organization has estimated that by 2020, MDD will be the second highest cause of disability worldwide (Lam et al, 2016).

Although there are many evidence-based treatments available, Canadian and international guidelines recommend antidepressant medication as first-line treatment for moderate to severe episodes of MDD (Kennedy et al, 2016). Once patients are in symptom remission after acute treatment with antidepressants, maintenance treatment is recommended for at least 6 to 9 months because of risk of relapse (Kennedy et al, 2016).

Recent meta-analyses of randomized controlled trials (RCTs) have confirmed that maintenance antidepressants are effective to prevent relapse (Sim et al, 2015). Despite this evidence, however, patients often decide to discontinue antidepressants after acute treatment. Some reasons for discontinuation include persistent side effects such as sexual dysfunction and weight gain, adverse effects with long term use of antidepressants (e.g., osteoporosis, gastrointestinal bleeding, risk of drug interactions with medications for other medical conditions). Patients also generally prefer a non-pharmacological treatment for depression. Hence, a priority question for patients is whether non-pharmacological treatments can be substituted for antidepressants for maintenance treatment.

Light therapy is a safe, evidence-based, non-pharmacological treatment for MDD and seasonal affective disorder (SAD) with fewer side effects than antidepressants. Light therapy consists of daily exposure to bright light, usually administered at home with a low-cost light device (Lam and Tam, 2009). The antidepressant effect is mediated through the eyes (and not skin exposure), so patients must be awake while using light therapy (Lam and Tam, 2009). The safety and efficacy of light therapy suggest that it would also be effective for maintenance treatment and relapse prevention in SAD or nonseasonal MDD. Unfortunately, however, there are few data on the continued use of light to prevent relapses (Nussbaumer-Streit et al, 2019).

We are planning to conduct a randomized relapse prevention trial to determine if light therapy can be substituted for antidepressants as a maintenance treatment for patients with MDD who are in remission after acute treatment and who wish to discontinue medications. Because there are no previous studies of light therapy for relapse prevention, there are unanswered questions regarding recruitment and feasibility for the study design.

In this feasibility study, we propose an important question: What factors will affect participant adherence to the daily use of light therapy for maintenance treatment? To answer this question, we will conduct a pilot study of open-label treatment with light therapy in a small sample (n=10) of participants meeting eligibility criteria to determine what factors will challenge or enhance adherence to the planned light therapy protocol. The results will provide essential information on recruitment and light therapy to provide guidance for the future randomized study protocol.

Methods

Eligible participants will provide informed consent to join this 12-week open-label trial. Participants will be given standardized verbal and written instructions to use a standard light device at home 5 days a week. After two weeks of light therapy to assess for adverse effects, participants will taper off their antidepressants. Outcome measures will be evaluated at monthly assessments and include validated measures

of depressive symptoms, functional impairment and quality of life. Participants will also remotely complete weekly online assessments.

Setting and Recruitment

Participants will be recruited from the Mood Disorder Centre and by advertisement. Some study visits (e.g., baseline, study termination, and relapse assessment visits) will be conducted at the Mood Disorder Centre outpatient clinic in the Djavad Mowafaghian Centre for Brain Health, but most assessment visits will be virtual (i.e., via Zoom and online surveys).

Participants

Ten participants will be recruited who meet the following eligibility criteria: [1] Outpatients 19 to 65 years of age; [2] DSM-5 criteria for MDD past or recurrent episode as determined by the Mini International Neuropsychiatric Interview; [3] taking an antidepressant for no more than six months; [4] participant desire to discontinue antidepressant treatment because of adverse effects or other reasons; [5] total score ≤10 on the clinician-rated Montgomery-Asberg Depression Rating Scale [MADRS]; [6] Willing and able to complete self-report and online assessments including sufficient fluency in English.

Exclusion criteria: [1] Any psychiatric diagnosis other than MDD that is considered the primary diagnosis, including Bipolar I or Bipolar-II (lifetime); [2] MDD with psychotic features (lifetime); [3] significant personality disorder diagnosis [e.g., borderline, antisocial]; [4] High suicidal risk, defined by clinician judgment; [5] History of drug or alcohol abuse, with a severity of at least moderate or severe within 6 months before screening; [6] Significant neurological disorders, head trauma, or other unstable medical conditions; [7] regular use of psychotropic medication other than an antidepressant or benzodiazepines (e.g., antipsychotics, mood stabilizers); [8] history of severe withdrawal effects with antidepressant discontinuation; [9] retinal disease or other eye condition preventing use of bright light therapy; [10] use of photosensitizing medication within 1 week of baseline visit.

Treatment

Light Therapy: The active treatment consists of daily exposure to a standard light device (e.g., fluorescent light box such as the Carex Day-Light Classic, emitting 4000 Kelvin white light rated at 10,000 lux at 14 inches from screen to cornea, with an ultraviolet filter) for 30 minutes as soon as possible after awakening, preferably between 7:00-8:00 am. Patients will be given standardized verbal and written instructions to use the light device at home 5 days a week (Monday to Friday) for the 12 weeks of the study. Adherence will be monitored using daily logs of device treatment times completed by patients.

Antidepressant Tapering: After using light therapy for 2 weeks (to assess potential adverse effects), participants will taper off antidepressants according to a standardized clinical algorithm, which addresses potential discontinuation effects. We are experienced with discontinuing antidepressants with patients, although we anticipate that any discontinuation symptoms will be mild and transient since participants in this study will have taken antidepressants for less than 6 months. Participants will be assessed every 2 weeks until antidepressants are stopped, and thereafter every 4 weeks till the end of the study.

Outcome Assessments

Clinician assessments to be completed at baseline (Week 0), Week 4, Week 8, Week 12, and/or study termination visits:

1) Montgomery Asberg Depression Rating Scale (MADRS)
2) Clinical Global Impression – Severity (CGI-S)
3) Concomitant medications
4) Adverse Events
5) Toronto Side Effects Scale (SES)
6) Discontinuation Emergent Symptoms and Signs (DESS) scale

Participant self-report measures to be completed during baseline (Week 0), Week 4, Week 8, Week 12, and/or study termination visits (through a REDCap interface):

1) Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)
2) Generalized Anxiety Disorder 7-item (GAD-7);
3) British Columbia Cognitive Complaints Inventory (BC-CCI);
4) Pittsburgh Sleep Quality Index (PSQI);
5) Sheehan Disability Scale (SDS);
6) Frequency, Intensity, and Burden of Side Effects Rating (FIBSER);
7) Adverse Events Scale, Self-Rated;
8) Lam Employment Absence and Productivity Scale (LEAPS);
9) Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q);
10) World Health Organization Quality of Life Short Version (WHOQOL-BREF);
11) EuroQol Group; 5 dimension; 5 level (EQ-5D-5L);
12) Healthcare Economic Assessment (HEA).

Participant measures to be completed at study termination visit (end of study at Week 12 visit, early termination, or the relapse assessment/verification visit).

1) CNS-VS computerized cognitive assessment (also at baseline);
2) Exit questionnaire regarding adherence factors for light therapy;
3) Semi-structured qualitative interview focused on issues of adherence.

Summary of Visits

Week -1	Week 0	Week 2	Week 4	Week 8	Week 12	Any time	Week +1
Zoom	At clinic	Zoom	Zoom	Zoom	At clinic	At clinic	At clinic
Screening	Baseline				Study end	Relapse assessment visit	Relapse verification visit
	Start light therapy	Start medication taper	Stop medication		End light therapy		

Assessment of Relapse

Participants will complete the PHQ-9 self-rated depression rating scale each week online. If the weekly PHQ-9 total score is ≥10, a relapse-assessment visit will be scheduled as soon as possible to determine if patient meets criteria for relapse.

Relapse will be defined as any of the following: [1] MADRS total score ≥22 for at least 2 consecutive weeks. If the relapse criterion of MADRS total score ≥22 is met at a scheduled assessment visit or an unscheduled relapse-assessment visit, an additional visit (i.e., the relapse-verification visit) will be scheduled within 1 to 2 weeks to verify the relapse; [2] Hospitalization for worsening of depression; [3] Suicidal ideation with intent, or suicidal behavior; [4] Any change in treatment (e.g., starting an antidepressant).

Subjects who relapse but do not require a Relapse Verification Visit (i.e., they meet relapse criteria other than that based on the MADRS total score) will complete the First Symptom of Relapse -- Self Assessment (FSR-SA). Any relapse event will be communicated by the study physician to the subject's treating physician.

Outcome Measures and Analysis

The primary feasibility outcome will be [1] rate of adherence (>75% of total daily sessions) to light therapy during the 12-week follow up. Secondary feasibility outcomes include patient factors that may challenge or enhance adherence, obtained via the exit questionnaire and qualitative interviews conducted at the end of the study. Secondary clinical outcomes include changes in MADRS and other outcome measures from baseline to end of treatment. Descriptive and appropriate statistical tests will be used for the analysis.

Qualitative/mixed methods: Semi-structured interview questions will be developed with specific exploratory interview probes created for participants showing higher or lower levels of adherence (determined on the basis of the quantitative data), as appropriate. All interviews will be digitally recorded,

transcribed verbatim, and a coding framework developed. Interpretative description, a qualitative methodology developed to generate knowledge relevant for the clinical application will be applied as the analytic framework. As is standard in qualitative methodology, data analysis will begin with the delivery of the first interview and proceed concurrently; summaries of the main factors relating to adherence or non-adherence will be created, and an interpretive account constructed.

Given our mixed methods approach, a sample of 10 participants will allow us to determine whether patients are likely to adhere to light therapy for 5 days a week over a longer term duration. The 12-week follow up duration for the pilot study, although shorter than the 12-month follow up planned for the proposed randomized trial, balances the pragmatic need to complete the pilot before the planned date for submitting the randomized study grant.

Potential Benefits and Potential Risks

As in all studies occurring in a clinical environment, the risk-benefits analysis must be carefully considered. The risks to the subjects identified in the study include: the risk of adverse or serious adverse reactions to the light therapy; the risk of discontinuation/withdrawal symptoms from antidepressant tapering; the risk of depressive relapse if the light therapy is not effective as maintenance treatment; the risk that the evaluations and questionnaires used in this study may make subjects feel uncomfortable or upset.

If a participant experiences a depressive relapse, the study doctor may advise the participant's family physician and/or regular psychiatrist in re-evaluating the current treatment being received. A participant experiencing acute distress (with immediate risk of self-harm) will be assisted by the study team following a standard operating procedure that could include developing a safety plan, and/or arranging for hospitalization or other medical care, among other actions.

Tests/questionnaires might provoke mild psychological distress in subjects, who can decline to provide answers if they do not feel comfortable responding. Psychological/cognitive testing might also be anxiety-provoking for subjects owing to concerns about performance and possible errors. However, no negative effects are expected to persist beyond the visits when subjects are completing testing for this study.

Potential benefits to the subjects include careful medical monitoring, and safely discontinuing antidepressants. However, no benefits from this study can be guaranteed.

Risk Management

We have standard operating procedures in place to ensure safety of participants. Participants showing clinical worsening or emergence of suicidal ideation during the trial will be withdrawn from the study and treated with standard clinical care.

If needed, clinical visits (via Zoom or at clinic) can be arranged at any time during the study period. At the end of the study, participants will be provided with psychiatrist recommendations for further care. Participants may continue with light therapy by purchasing a light device (retail cost $150-$300).

Confidentiality and Data Security

Ethical approval for the study will be obtained from the UBC Clinical Research Ethics Board. Participants will provide informed consent.

Research Electronic Data Capture (REDCap) is a web-based system for data collection where participants will complete the self-report questionnaires and enter data in a web browser from remote locations. REDCap includes a complete suite of features to support Health Insurance Portability and Accountability Act (HIPAA) compliance, including a full audit trail, user-based privileges, and integration with the institutional server.

The virtual visits are conducted via UBC Zoom, which has been approved by Vancouver Coastal Health for both privacy and security. Participants will receive the standard Zoom disclosure and information form as approved by Vancouver Coastal Health.

References

Kennedy SH, Lam RW, et al. CANMAT 2016 clinical guidelines for the management of adults with major depressive disorder. Section 3. Pharmacological treatments. Can J Psychiatry 2016; 61:540-560.

Lam RW, McIntosh D, et al. CANMAT 2016 clinical guidelines for the management of adults with major depressive disorder. 1. Disease burden and principles of care. Can J Psychiatry 2016; 61:510- 523.

Lam RW, Tam EM. A Clinician's Guide to Using Light Therapy. Cambridge University Press, 2009.

Nussbaumer-Streit B, Forneris CA, et al. Light therapy for preventing seasonal affective disorder. Cochrane Database Syst Rev. 2019 Mar 18;3:CD011269.

Palay J, Taillieu TL, et al. Prevalence of mental disorders and suicidality in Canadian provinces. Can J Psychiatry 2019.

Sim K, Lau WK, et al. Prevention of relapse and recurrence in adults with major depressive disorder: Systematic review and meta-analyses of controlled trials. Int J Neuropsychopharmacol. 2015; 19.