DGIM Project Summary

Project Name: Practicing Alternative Techniques to Heal Depression: The PATH-D Study
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Principal Investigator:
Stuart Eisendrath, MD
UCSF Langley Porter Institute, Box 0984
401 Parnassus Avenue, Suite 278
Email: StuartE@lppi.ucsf.edu

Co-Investigators:
Mitchell Feldman, MD, MPhil
400 Parnassus Avenue Box 0320
UCSF Langley Porter Institute, Box 0320
Email: mfeldman@medicine.ucsf.edu

J. Craig Nelson, MD
UCSF Langley Porter Institute, Box 0320
401 Parnassus Avenue
Email: CraigN@lppi.ucsf.edu

Kevin Delucchi, PhD
UCSF Langley Porter Institute, Box 0984
401 Parnassus Avenue
Email: KDelucchi@lppi.ucsf.edu

Patricia Arean, Ph.D
UCSF Langley Porter Institute, Box 0984
401 Parnassus Avenue
Email: PatA@lppi.ucsf.edu

Zindel Segal, PhD
University of Toronto
Email: zindel_segal@camh.net

R. Scott Mackin, Ph.D
UCSF Langley Porter Institute, Box 0984
401 Parnassus Avenue
Email: ScottM@lppi.ucsf.edu

Margaret Kemeny, PhD
3333 California Street
Email: KemenyM@healthpsych.ucsf.edu

Primary Contact: Erin Gillung
PATH-D Study Project Coordinator
Email: ErinG@lppi.ucsf.edu

Research question(s):
The PATH-D Study aims to find an effective treatment for patients with treatment-resistant depression (TRD). Approximately 50% of patients with Major Depressive Disorder will fail to remit completely with two or more trials of antidepressants, thus suffering TRD. Because current treatment strategies for TRD are limited, new techniques are needed. This study is a randomized, controlled trial of Mindfulness-Based Cognitive Therapy (MBCT) versus Health-Enhancement Program (HEP) for the TRD population. Both arms of the study will continue to receive standard medication management treatment as usual (TAU) throughout the study. The goal of this research is to determine the efficacy of MBCT in reducing symptoms of depression in adults with treatment-resistant depression by testing the following primary hypotheses:

Hypothesis 1a. MBCT+TAU will be more effective than HEP+TAU in reducing depressive symptomatology (17-item Hamilton Depression Rating Scale, HAM-D17) [1]) in patients with TRD over a period of 8 weeks.

Hypothesis 1b. MBCT+TAU will produce a greater response rate (≥50% reduction in HAM-D17) than HEP+TAU in patients with TRD over a period of 8 weeks.
Hypothesis 1c. MBCT+TAU will produce a greater rate of remission (HAM-D$_{17}$ <8) than HEP+TAU in patients with TRD over a period of 8 weeks.

Secondary hypotheses and analyses include the following:

**Hypothesis 2. Effect on Functional Status:** MBCT+TAU will be more effective than HEP+TAU in reducing disability (12-item Short Form Health Survey [SF-12] [2]; Work and Social Adjustment Scale [WSAS] [3]), improving quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form [Q-LES-Q-SF] [4]) in patients with TRD.

**Hypothesis 3. Mediators of MBCT Efficacy:** The MBCT effect on depression (HAM-D$_{17}$, QIDS-SR$_{16}$) and functional status (SF-12, WSAS, Q-LES-Q-SF) will be mediated by enhanced mindfulness (Five Facet Mindfulness Questionnaire [FFMQ] [5], Toronto Mindfulness Scale [TMS] [6]), diminished rumination (Ruminative Response Scale [RRS]) [7, 8], and decreased experiential avoidance (Acceptance and Action Questionnaire [AAQ]) [9] and increased self-compassion (Self-Compassion Scale) [SCS].

**Hypothesis 4. Length of efficacy:** We will assess whether treatment gains in depression (HAM-D$_{17}$, QIDS-SR$_{16}$), functional status (SF-12, WSAS, Q-LES-Q-SF) and mindfulness (FFMQ, TMS), rumination (RRS), avoidance (AAQ) and increased self-compassion (SCS) are retained by 3, 6 and 12 months after the end of the MBCT and HEP interventions.

**Brief Background/Significance:**
Major Depressive Disorder (MDD) is the number one cause of disability in North America and is projected to become the second cause of disability worldwide by 2020 [10-12]. There is compelling evidence that TRD represents the greatest disease burden of depression [13], as a striking 50% of individuals with Major Depressive Disorder (MDD) will fail to remit with two or more adequate trials of antidepressant medications, thus suffering Treatment-Resistant Depression (TRD) [14-18]. The recent large scale Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial indicated that even after two full dose treatment attempts, 50% of the initial cohort of patients continued to suffer with TRD. The response and remission rates for psychotherapy treatment alone appears similar to medication trials [19-21]. Furthermore, individuals who do not respond to initial treatments often suffer adherence difficulties [22, 23]. TRD is associated with even greater disability, mortality, morbidity, somatic symptoms, risk of relapse and societal cost than those who suffer from non-resistant forms of depression [13, 24, 25].

**MBCT** is a recently developed group treatment that integrates mindfulness meditation training with some elements of Cognitive Behavioral Therapy (CBT) [26]. It has been found to be effective in preventing relapse in individuals in complete recovery from depression. This group-based, 8-week intervention uses mindfulness meditation as its core therapeutic ingredient and trains people to have a different relationship to depressive thoughts and feelings. The program teaches skills that allow patients to disengage from habitual (“automatic”) dysfunctional thoughts, such as depressive ruminations, as a way to reduce future risk of relapse and recurrence of depression [27]. Meditations such as Body Scans, mindful movement, and sitting meditations help participants to become more aware and accepting of thoughts, moods, and sensations. In open, nonrandomized, pilot studies conducted at UCSF [28], MBCT has been found to significantly reduce depressive symptoms in TRD. The PATH-D study was designed to evaluate MBCT’s efficacy in a randomized, controlled trial. MBCT appears to be a complementary and alternative medicine (CAM) intervention that is in step with public demand for treatment innovation and learning skills to help empower self-regulation of mood.

**HEP** was developed as a collaborative effort between the Waisman Laboratory for Brain
Imaging and Behavior at the University of Wisconsin – Madison and the University of Wisconsin Health: Integrative Medicine Program in consultation with the National Center for Complementary and Alternative Medicine (NCCAM), to serve as a control condition for studies of MBSR [29]. It has been shown to decrease global stress levels on the SCL-90 and to increase perceived health. As stress has been considered a contributor to depression, HEP may have potential to reduce depressive symptoms. HEP was designed to provide real health benefits to participants but omit mindfulness components. The program is designed to increase health and overall well-being by focusing on four health domains. These include: (1) Music Therapy (2) Nutrition (3) Physical Activity including, walking and stretching and (4) Functional Movement.

This study represents the first clinical trial to expressly evaluate a mindfulness-based cognitive therapy for MDD and utilizes HEP, a credible, health promoting group intervention as a control intervention. The heuristic significance of this study is that it evaluates the putative mediators of MBCT (mindfulness, decreased rumination, increased acceptance and decreased avoidance, and enhanced self-compassion) as the agents producing acute relief of TRD. Clinically, this study represents the potential to identify an effective treatment for a major public health problem and to diminish suffering.

Inclusion/exclusion criteria (list)

Inclusion Criteria:
- DSM-IV TR Diagnosis of Major Depression currently receiving medication management
- Adequate trial of 2 or more antidepressants (one of which at UCSF) documented by patient report, chart review and/or STOR
- HAM-D17 score ≥ 14
- Any Ethnicity
- English Speaking
- Male or Female
- No current psychotherapy (i.e. only medication management treatment) or plan to start new psychotherapy during MBCT or HEP
- Age 18 to 80

Exclusion Criteria:
- Bipolar Disorder, Obsessive Compulsive Disorder, Schizophrenia, Schizoaffective Disorder, Antisocial and Borderline Personality Disorders (with active self-harm such as cutting behaviors), Pervasive Development Delay
- Any psychosis
- Active suicidality as defined by having current intent and/or plan
- Meditation Practice once or more per week; yoga more than twice per week at study entry
- Current Substance Abuse Disorder (e.g. Current regular illicit drug usage, prescription drug misuse, or drinking 3 drinks per day for women or ≥ 4 drinks per day for men.)
- Cognitive Disorder with Mini Mental Status Exam score ≤ 25
- Medical illness rated 4 on Cumulative Illness Rating Scale (e.g. confined to a wheelchair) which would interfere with the ability to participate in HEP.

The below portion is a proposal that pending, preliminary approval from the DGIM review board will be submitted to the UCSF IRB Committee for review and approval.

With prior authorization, study research assistants (RA’s) or other authorized research staff will access the STOR system to identify potential patients that may be eligible for our study.
We will identify English speaking patients with current depression by pulling patients who have depression listed on the problem list and/or with a relevant ICD-9 diagnosis and documentation of being prescribed an antidepressant. DGIM practitioners (including attending and resident physicians and nurse practitioners) will then be notified via a “Dear Caregiver” letter (attached) that their patient may be eligible for our study. At that point, if the physician determines their patient IS NOT a good candidate for our study (i.e. due to medical disability, frailty, cognitive impairments, etc), they will indicate this on a designated area of the recruitment letter and return it to our study team using intercampus mail. After two weeks, if the research team has not been notified of patient ineligibility, they will send a “Dear Patient” recruitment letter (attached) to the patient notifying them of the PATH-D Study and their potential eligibility for treatment. The letter will specify that when study staff call to discuss the project, they will not specify the intention of the call or mention the patient’s depression to anyone other than the potential study candidate. Potential participants will indicate on the designated area of the recruitment letter whether or not they wish to be contacted by a research assistant to discuss possible participation in the PATH-D study. Patients can check off a “Yes” or “No” option and mail their response back to the study team in the provided pre-addressed, pre-paid envelope. Interested patients will be contacted immediately by a staff member to determine interest and eligibility, while those patients declining interest will not be contacted any further. Staff members will use an IRB-approved recruiting script (attached). If a response is not received within two weeks, a call will be made to the patients who have not responded to inquire about participation and provide information about the study using the IRB-approved recruiting script.

The following narrative describes the currently approved (CHR# H5270-32986-02) recruitment protocol targeting the UCSF Langley Porter Psychiatric Institute (LPPI):

Participants are recruited via an established research registry used in the LPPI intake process, through mental health provider introductions, and through flyers located in LPPI outpatient clinics. New patients are currently asked to enroll in a CHR-approved research registry which authorizes researchers to examine patient medical records for the purpose of determining possible eligibility to enroll in research. A study RA will examine records of patients who had previously agreed to participate in this registry and contact them by phone accordingly. As part of standard clinic intake procedures, patients also complete a 20-minute computerized Electronic Health Inventory that includes psychiatric symptoms, health conditions, and other health questions. The RA will identify all eligible patients based on their endorsement of elevated depression symptoms and psychiatric history.

Patients who have not agreed to be part of the research registry will not be considered by the research team. However; they may be approached by their provider who will be informed of the study through an IRB approved “Dear Doctor Letter.” In addition to that letter, providers will be supplied with an approved “Dear Patient Letter” to explain the study and to request approval to be contacted by a research team member. If patients would prefer not to be contacted directly, the “Dear Patient Letter” gives the option of having patients contact the research team instead. In this case, a flyer will be given to patients describing the study and providing contact information for Dr. Eisendrath and his research team.

All eligible patients who have given permission will be contacted within two weeks of clinic intake by telephone directly by the research assistant, who will use a IRB approved Telephone Recruiting Script to describe the study and, if patients agree, to schedule an appointment. At the appointment, the RA will further explain the study and obtain informed consent. If patients do not enroll, they will continue to receive their usual medical and mental health services and care will not be affected. If patients consent to participate in the study, the RA will conduct an intake evaluation to identify patients who may be eligible for the study.

Benefits/burden for participants (clearly identify potential for harm):
If this study demonstrates MBCT as an effective intervention for TRD, the public health
impacts would be substantial. Individual participants may benefit from learning MBCT techniques aimed at helping them change their relationship to depressive thoughts and feelings free of charge. This may significantly reduce depressive symptoms. In our pilot study of 54 patients, participants experienced a significant decrease in depressive symptoms during the 8 week course of MBCT. We expect participants receiving MBCT in this study may experience similar benefits. The work of Teasdale [30] and Ma and Teasdale [31] also suggests that MBCT is effective at reducing future depression relapses. So participants may experience not only a decrease in symptoms, but also a lower risk of future episodes through their participation. Individuals randomized to HEP may benefit from the group support and social cohesion, which are nonspecific factors that this study is designed to test. Moreover HEP has been shown to diminish stress, considered an important contributor to depression. Even if their depression does not improve, participants may benefit from being able to subsequently take the MBCT course at no charge at the end of their follow-up period if they elect to do so. Participants in both groups may also benefit from knowing that they are contributing to a research project designed to enhance understanding of depression.

The primary risk of participation in this study is that participants will be investing a significant amount of their time in the form of the MBCT and HEP classes and the assessments. However, this investment may not lead to a greater improvement in mood status than with TAU alone. This risk may be offset by the potential benefit of MBCT or HEP on mood status, the modest monetary payments ($250) for the completion of study assessments and the reward of participants feeling that they are contributing to a research endeavor.

Another risk is that individuals could become more depressed in undergoing the MBCT and HEP courses. Natural course of depression or intercurrent life event may worsen depression severity. In addition, individuals may become frustrated over learning the techniques of MBCT or HEP although, this has not been evident in pilot trial of either intervention. These issues, however, are actively addressed in the MBCT course, so that participants are encouraged to voice these frustrations in the MBCT groups and develop solutions in that setting. In HEP, the leaders are active in adjusting the techniques to the individual, so that frustrations should be minimized. Moreover, if depressive symptoms worsen over the course of 8 weeks, safety mechanisms have been established to identify these cases, stabilize treatment and make clinical referrals and/or stop treatment according to recommendations of trained clinical staff. These mechanisms have been outlined in detail in the attached suicide assessment protocol.

Although a rare occurrence, participants may also become uncomfortable being asked questions about their mood and disability during assessments. In the event that interviews become too upsetting for participants to continue, we will stop the interview and provide counseling to stabilize the participant.

Another potential risk for participants is that by participating in the study they will be agreeing to defer starting an alternative form of psychotherapy. This risk will be mollified by participants being free to start an alternative psychotherapy and elect to withdraw from the study, although they will be allowed to complete the group classes if they wish to do so, in order to enhance reporting new treatments. Moreover, since participants will be drawn from patients who are only receiving medication management in their clinical care, they will already have elected not to pursue psychotherapy. Thus avoiding a new psychotherapy for 8 weeks (other than the MBCT for those in that arm) does not appear likely to be a significant limitation. If patients would like to initiate psychotherapy during the course of this study an appropriate referral will be made.

**Any benefits or burden to DGIM practitioners?**

Because many patients seen in primary care clinics do not utilize or have adequate access to
mental health treatments, **those patients diagnosed with major depression and receiving antidepressants for its treatment will have the opportunity to participate in either the MBCT or HEP intervention at no cost and will receive $250 for completing all assessments.** The benefit to the DGIM practitioners is the opportunity to augment depression medication management with two interventions that may significantly lessen depression. The PATH-D Study will provide practitioners with a free, augmentative treatment option for their patients who are currently being prescribed antidepressants as a primary method to treat symptoms of depression. Pilot studies indicate that there is little likelihood of burden from worsening with these interventions. However, all patients will be monitored with weekly depression rating scales during the active 8-week treatment and at regular intervals for one of follow-up. If the research team identifies that a patient’s symptoms of depression are worsening (an identified risk outlined above), DGIM practitioners will be contacted and notified of their patient’s mental health status and treatment outcomes and/or referrals will be made within the community or UCSF if deemed clinically appropriate.

Additionally, the recruitment techniques described above have been designed to minimize potential burdens upon practitioners so that the primary efforts will be expended by the research team.

**Timeline for recruitment (projected start and stop dates)**
The study is expected to last four years from the time that first year funds were received (3/1/09) to recruitment and data collection completion (2/28/2013). The first 6 months of the funding period has been dedicated to hiring and training staff, finalizing study protocols and starting initial subject recruitment. Official recruitment activities began on 8/31/09 and will last for approximately 30 months or 2.5 years until all 124 participants have been enrolled into treatment. To meet our recruitment goals, we plan to enroll approximately 2 patients per week at a rate of 8-10 patients per month. At this rate, we anticipate all patients will have completed 8 weeks of either MBCT or HEP training and completed the final 52 week follow-up assessment so that data collection will be finalized by 3.75 years. Thereafter, we anticipate a 6-month period for data analysis, scientific articles preparation, and further grant submissions.

**Funding source:** National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH).

**Potential for DGIM collaborators? (We encourage DGIM resident and fellow involvement in particular)**
Mitchell Feldman, MD, MPhil.is a Co-Investigator in this investigation. By utilizing the DGIM population, this study will replicate the STAR*D study population which compared depressed patients receiving treatment in a psychiatric setting as compared to a primary care setting. Moreover, the DGIM site adds to the socio-cultural diversity that is limited at the Langley Porter site.

**Do you agree to notify us when recruitment is completed?**
Yes

**Date form completed**
October 2, 2009
References