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Challenges and Solutions for Depression Prevention Research: Methodology for a Depression Prevention Trial for Older Adults with Knee Arthritis and Emotional Distress

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Abstract

Objectives—To describe the methodology, challenges, and baseline characteristics of a prevention development trial entitled “Reducing Pain, Preventing Depression”.

Design—Sequential multiple assignment randomized trial (SMART) comparing sequences of cognitive behavioral therapy (CBT) and physical therapy for knee pain and prevention of depression and anxiety. Participants were followed for 12 months for new episode depression or anxiety.

Setting—Late-Life Depression Research Clinic.

Participants—Individuals 60 and older with knee osteoarthritis and subsyndromal depression, defined as PHQ-9 score of at least “1” (which included the endorsement of one of the cardinal symptoms of depression [low mood or anhedonia]), and no diagnosis of MDD per SCID.

Intervention—Sequential randomization to CBT, physical therapy, or enhanced usual care.

Measurements—Depression and anxiety severity and characterization of new episodes were assessed with the PHQ-9, GAD-7, and the PRIME-MD. Knee pain was characterized with the Western Ontario McMaster Arthritis Index. Response was defined as at least “Very Much Better” on a Patient Global Impression of Change.

Results—At baseline (n=99), average age=71, 61.62% are female, and 81.8% are Caucasian. The average PHQ-9 = 5.6 and average GAD7= 3.2. The majority were satisfied with the interventions and study procedures. We describe the challenges and our solutions which will be used in a confirmatory clinical trial of efficacy.

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Conflicts of Interest: Receipt of medication supplies for investigator-initiated studies from Pfizer and Reckitt Benckiser. Dr. Butters served as a consultant for GlaxoSmithKline from whom she received remuneration for participating in cognitive diagnostic consensus conferences for a clinical trial; the remaining authors report no disclosures.

Conclusions—A SMART design for depression and anxiety prevention, utilizing both CBT and physical therapy, appears to be feasible and acceptable to participants. The methodological innovations of this project may advance the field of late-life depression and anxiety prevention.

Keywords

DEPRESSION; PREVENTION; PAIN; ANXIETY; LATE-LIFE

Introduction

Medical illness, functional disability, family and personal histories of mood disorders, social isolation, life stressors, bereavement, and neurodegenerative disorders are all putative risk factors for new onset major depressive disorder (MDD) and anxiety disorders in older adults. Osteoarthritis (OA) pain and associated disability are risk factors for a major depressive episode and possibly anxiety disorders,[1] and treating OA pain and disability may reduce the severity of comorbid MDD and anxiety.[2] Indeed, among older adults with MDD, a significantly higher proportion report pain that is disabling compared to those without MDD.[3] Patients living with both conditions also have significantly worse health-related quality of life, greater somatic symptom severity, and higher prevalence of other pain disorders than chronic pain patients without depression.[4] It is plausible that reducing pain and disability could actually prevent new onset cases of MDD and anxiety disorders, although this has not yet been tested. Since anxiety disorders increase risk for MDD[5] and both conditions worsen comorbid medical burden and disability[6], prevention interventions should aim to reduce the risk of developing both depression and anxiety in late-life.

Learning-based interventions such as Cognitive Behavioral Therapy (CBT)[13] or a knee-specific physical therapy (Manual Therapy and Supervised Exercise[14]; EXERCISE) are routinely prescribed along with analgesics for both pain control and improved functioning. Both CBT and EXERCISE are behaviorally activating, improve self-efficacy, and reduce learned helplessness.[15] These qualities make them rational choices for a prevention study of new episode MDD and anxiety disorders.

The order effect of these interventions on preventing MDD and anxiety disorders is also not known. Initial exposure to CBT may enhance attention to psychological health, motivation, and problem solving, thus enabling individuals who are first exposed to CBT to make better use of EXERCISE (compared with those exposed to EXERCISE followed by CBT). This order effect, however, is not established. Indeed, exposure to EXERCISE before CBT may engage participants who are otherwise not psychologically minded, preparing them to be more open to a psycho-behavioral intervention such as CBT. Since the clinical approach for non-responders to an intervention usually involves continued exposure or a switch, testing sequences of interventions is indicated to inform care.

Implementing and testing such complex interventions entails substantial methodological and logistic challenges; this is especially the case among older adults in whom individual variability is high and, often intervention tolerance may be low because of frailty or other geriatric-specific syndromes. Using a sequential multiple assignment randomized trial (SMART)[16] approach, we are attempting to address this set of unique methodological

challenges as we seek to prevent new onset depression and anxiety in older adults with knee osteoarthritis. In order to guide future protocols, we describe here the trial methodology, intervention development, and procedural challenges and solutions experienced during the course of this study.

Methods

Overall Study Design and Specific Aims

This is a two-stage adaptive treatment design project. Stage 1 compares the relative effectiveness of 8 sessions of CBT, 8 sessions of EXERCISE, and Enhanced Usual Care (EUC[17,18]; the control condition) (Figure 1). Non-responders to stage 1 then proceed to stage 2 in which they may be randomized to 8 sessions of the alternative intervention or 4 additional sessions of the intervention received during stage 1. All participants are then followed for 12 months after the end of their final intervention for new episodes of MDD and anxiety disorders. The overarching aims are to 1) develop a patient-centered new onset depression and anxiety prevention intervention for older adults living with knee osteoarthritis (CBT), 2) explore if improving pain and disability prevents new onset MDD and anxiety disorders during one-year follow-up among at-risk seniors with knee OA, and 3) permit an estimation of relative effectiveness of CBT, EXERCISE, and EUC as well as order-effects of the active prevention interventions. We also plan to follow participants receiving EUC to obtain benchmark estimates of new episode MDD and anxiety disorders.

Participants

Our target enrollment was 135 participants > 65 years old. While pain and associated disability are risks for depression, the majority of individuals living with these problems do not become depressed or anxious. This led us to a blended selective/indicated approach to depression and anxiety prevention by including individuals most at risk of new onset depression and anxiety disorders – those with subthreshold symptoms. Thus, in addition to having knee arthritis, participants also endorsed symptoms of subthreshold depression as determined by the 9-item Patient Health Questionnaire (PHQ-9)[19] scores of at least “1” (with one of the cardinal symptoms of depression [low mood or anhedonia] endorsed for at least several days for the past 2 weeks, and no diagnosis of current or partial remission MDD as determined by the Structured Clinical Interview for DSM-IV (SCID)[20] interview). Participants could have a history of major depression and anxiety disorders, but not within the past 12 months. Including subjects with recent disorders would confuse the prevention of a new episode from the treatment of a partially remitted earlier episode.

Sources of recruitment include primary care, online, print, and radio advertisements, and university-affiliated research registries. After recruiting the first four participants for iterative development of CBT (see below), we began recruitment of the next 131 participants for Stage 1 of the adaptive prevention study. The inclusion and exclusion criteria and rationale for each entry criterion are listed in Table 1.

Interventions

Randomization and Sequence of Interventions—We use permuted block randomization with the list of consented participants maintained by the data manager. Participants are randomized using a 2:2:1 allocation (i.e., 2 participants randomized to either CBT or EXERCISE for every 1 subject randomized to EUC). As this is treatment development work, our reason for this allocation procedure is to gain more clinical experience with CBT and EXERCISE. **Stage 1 for participants randomized to prevention interventions:** Simultaneous to receiving EUC (which is provided for all participants, see below), participants are randomized to receive 8 weeks of either CBT or EXERCISE. Each session lasts 45–60 minutes. CBT is delivered at the PCP's office, the offices of the Late-Life Depression Prevention Center, in the participant's home, or via SKYPE or telephone. The location of where CBT is delivered is documented, as these data inform feasibility and scalability. EXERCISE is delivered at the Clinical and Translational Science Institute for Physical Therapy, a state-of-the art rehabilitation facility staffed with master's and doctoral-level physical therapists. **Stage 2:** Stage 1 non-responders (defined below) are randomized to an additional 4 sessions of the same intervention or 8 sessions of the alternative intervention (Figure 1). This will allow us to explore if switching to a full dose of the alternative intervention or extending the current intervention is more efficacious for prevention. All participants, regardless of response status, are followed for 12 months for new onset MDD or anxiety disorder after completion of prevention interventions in Stage 1 or Stage 2, or for those randomized to EUC alone.

Enhanced Usual Care (EUC)—All participants, including those randomized to EUC, have information mailed to their PCP describing the best practice approach for providing analgesia for knee osteoarthritis.[21] For all participants, incidental findings during scheduled blinded assessments (i.e., new onset depression or anxiety or worsened pain or cognition) are relayed to their PCP. We acknowledge that while the choice and dosing of analgesics are not standardized, this approach reflects the array of medication regimens required for analgesia and provided in primary care, and is consistent with a collaborative care approach.[22] We track the type and dosage of both scheduled and as-needed medications (opioids and non-opioids) and other somatic interventions (e.g., acupuncture, injections).

Cognitive Behavioral Therapy for Pain (CBT)

Training the Interventionists—Clinicians experienced in providing manualized psychotherapy to older adults (supervised weekly by JQM) provide CBT. The intervention modules are: 1) combating demoralization; 2) teaching coping skills and problem solving techniques; 3) shifting self-view to that of an active, resourceful, and competent person and encouraging behavioral activation; 4) learning to alter associations between thoughts, feelings, and behaviors that do not promote analgesia and identifying how to change automatic, maladaptive thoughts; 5) learning relaxation skills; and 6) facilitating maintenance and generalization of skills. As insomnia is prevalent in older adults and those with pain, a modified version of Brief Behavioral Treatment of Insomnia (BBTI)[23] is included if participants score > 5 on the Pittsburgh Sleep Quality Index (PSQI) at baseline.[24] The inclusion of modified BBTI has not increased the number of sessions or exposure to CBT. Participants can decide to focus on BBTI instead of one of the other modules, in the

spirit of a personalized intervention. All CBT sessions are audiotaped and 20% then randomly selected for fidelity ratings by JQM to assure maintenance of treatment specificity and integrity.

Adapting and Revising the Intervention—To ensure intervention fidelity, we use group supervision and one-on-one feedback using evaluations of randomly selected 20% of audiotapes of CBT sessions. CBT adherence ratings assessing quality are completed by the intervention supervisor, using two sessions for each case — an early session (1–3) and a later session (4–8). Following a batch of ratings, corrective feedback is provided. We also developed a treatment fidelity scale to document the absence of intervention contamination effects. Using this scale, ratings are completed on seven consecutive minutes of the session starting five minutes into the session. Sessions are rated independently by two raters for the presence of CBT elements.

The content and ordering of the modules, components of the manual, and appearance and content of participant handouts were all reviewed and modified on a weekly basis over the course of the first 3 months of the project. Since this is an intervention development project, we assumed there would continue to be adjustments to the intervention as we continued to elicit feedback from the participants and clinicians. Indeed, during the course of the project, adjustments to CBT have been made to account for degrees of cognitive impairment, difficulty with movement, insomnia, and transportation. The principles of each module were articulated to the participants. Also, we developed graphics to communicate the content of and connections between modules and the gate control theory of pain[26] as well as the proposed mechanism via which each module may reduce pain and stress and improve functioning.

EXERCISE

The EXERCISE intervention is a combination of supervised exercise therapy and manual therapy techniques. The supervised exercise component represents state-of-the-art evidence-based practice guidelines[14,27,28] and combines aerobic and strengthening exercises.[14,27,28] The manual therapy techniques involve the application of manual force from the therapist.[29] These techniques include a series of motions of the tibia with respect to the femur that are needed for normal knee flexion and extension. The manual therapy techniques also include lower extremity stretching exercises delivered by the therapist. Detailed descriptions of the manual therapy techniques and intervention philosophy utilized in this study are available in manual therapy textbooks.[30] In addition, all participants are instructed in a home exercise program with the goal to be independent in the home exercise program by week 8.

Schedule of Assessments, Criteria for Response and Booster Sessions—Independent evaluators assess participants by phone or in person. Participants are assessed at six time points (T1-T6) (Table 2). We defined clinically significant response to the active interventions (unique from the primary aim of prevention of MDD and anxiety disorders as diagnosed with the blended PRIME-MD/MINI Neuropsychiatric interview) as 1) much better or 2) very much better on a Patient Global Impression of Change (P-GIC) that ranged from 1–7. The wording of the P-GIC is: “Check the circle that best describes how you have

felt overall since you began participating in this research study." We selected the P-GIC as criteria for response because since participants endorsed both knee pain and mild emotional distress, only using percent improvement of pain as the response criterion could miss other improvements valued by participants, such as improvement in insomnia, psychological stress, or self-efficacy. Pain, stiffness, depression, anxiety, and the Western Ontario and McMaster University Arthritis Index are also assessed at these time points. We plan to calculate degree of correlation between the P-GIC and each of these measures to learn more about whether these variables change in concordant directions.

Responders to Stages 1 and 2 are followed for 12 months (from the end of the intervention) for conversion to new onset MDD or anxiety disorder. Based on work by Rovner,[31] responders receive booster sessions at 6 and 9 months following the end of the prevention intervention(s). If participants receive both interventions, then they can select the booster session they prefer. Stage 2 non-responders are referred to their PCP with pain treatment recommendations (based on expert guidelines). Non-responders are also followed for 12 months for the development of new onset MDD or anxiety disorder.

Planned analysis—Cox regression models will be used to assess whether study groups differ reliably on risk of the outcome events (MDD and anxiety disorders), adjusting for participant characteristics as needed. We also plan to estimate the number needed to prevent, with a 95% confidence interval, comparing CBT, EXERCISE, and controls who received EUC. Since the actual number of "events" (e.g., incident syndromal depression or anxiety) may be few, we will also explore changes in symptoms severity, using continuous measures of depression and anxiety. To assess a difference in reduction in pain, we will use Kaplan-Meier methods to report the estimated percentage of participants achieving the endpoint over time, defined as at least a 30% improvement on the pain subscale of the WOMAC. The log-rank test will be used to test the primary event across the three groups (CBT-P, EXERCISE, and EUC).

Considering that we are using SMART methodology,[16] we will also use statistical methods for dynamic treatment regime (also known as adaptive treatment strategy) to compare sequenced interventions. Specifically, we will estimate the effect of treatment sequence "Treat with CBT-P for 8 weeks, if does not respond, use EXERCISE intervention" in reducing pain compared to other sequences. For these comparisons, we will use inverse-probability-weighting and g-estimation.[33,34]

Early Results

Recruitment

As of December 2014, we have recruited 73% (n=99) of our expected sample (Figure 2). Because of a delayed start, the need for 12 months of follow-up, and the fact that this is a treatment development and not efficacy testing experiment, we halted recruitment at this time. Forty-seven percent of screened participants have been recruited from direct-to-consumer advertisements (radio, newspaper, and advertisements on public transportation), university-affiliated late-life research registry (32%), primary care (8%), and other sources (13%). These sources of recruitment are different from our recently completed depression

prevention study of older adults living with high emotional stress in which 45% were recruited from primary care and approximately 20% were recruited from community outreach endeavors.[35] The percentage of individuals who phoned in and were screened over the phone found to be ineligible for further evaluation was 74%. The primary reasons for ineligibility were knee pain not severe enough (28%), items 1 or 2 on the PHQ-9 (depressed mood or anhedonia) not endorsed (21%), PHQ-9 score = 0 (18%), and currently taking an antidepressant and not willing to discontinue it (11%). Table 3 lists descriptive characteristics of participants at baseline.

Participant Satisfaction

Following T6 (12 months), participants are asked to complete a brief satisfaction survey. The survey questions, rated on a scale from highly dissatisfied to highly satisfied, were created to inform the success of future studies by assuring the interventions are patient-centered and that participants are satisfied with: 1) flexibility in scheduling appointments; 2) helpfulness of the therapist; 3) frequency of appointments; 4) usefulness in managing pain; and 5) usefulness in managing stress. The survey also includes a free text box where participants can share their thoughts about how the project can be improved. Table 4 summarizes these data to date.

While in general the responses were positive, the results indicated there may be room for improvement in management of pain. However, the average score ranged between satisfied to highly satisfied, and given the challenge of treating chronic pain, this is encouraging. The free text responses suggest varying degrees of satisfaction with the project. We have used these responses to: 1) be more direct about the mental illness prevention goals of the study, since at least one subject felt we were using knee pain as a “hook” to enroll participants; and 2) during the consent process, more explicitly describe how we think CBT may help with both pain control and prevention of both MDD and anxiety disorders.

Lessons Learned and Adjustments Made During the Course of the Project

Since this prevention intervention development project is a blend of public health (prevention of depression) and clinical care (improving knee pain and disability) and is being conducted in preparation for a confirmatory R01, we expected that many changes to the protocol would be required during the project. Table 5 lists the many challenges to the successful implementation and completion of the protocol and how we resolved these challenges without compromising internal validity. Our multidisciplinary team meets on a weekly basis during which methodological and procedural issues from ongoing trials are discussed. Solutions to challenges are discussed among the staff (who usually bring the challenges to the meeting), the principal investigator, and biostatistician. Using this approach we address the feasibility and burden concerns of staff while assuring the specific aims of the PI are being met and that any adjustments to the protocol will not interfere with the analytic plan. Many of the challenges described in Table 5 can be categorized as: 1) minimizing subject burden; 2) optimizing retention and minimizing early attrition; 3) minimizing missing data and adding assessments; 4) adjusting time frames during which data may be collected; 5) assuring participant safety; and 6) addressing threats to internal validity of the study such as assuring entry criteria are met before randomization.

Discussion

Two unique qualities of this depression prevention project deserve highlighting. First, this may be the only study of depression prevention to utilize formal SMART methodology. Such trials are individually tailored interventions that specify how the intensity or type of treatment should change depending on the participant's needs. For example, this project will guide our understanding of how such interventions for prevention of depression and anxiety disorders can: 1) Adapt treatment to a patient's chronic and/or changing course; 2) Deliver appropriate treatment when needed most; 3) React to non-adherence or side-effect profiles; 4) Reduce treatment burden and deliver only what is necessary; 5) Deliver early treatments with positive and durable downstream prevention effects; and 6) Sift through available treatment options.[16] This may lead to more personalized prevention care over time.

The second characteristic which distinguishes this prevention project from others is the utilization of a unique multidisciplinary team approach. Our clinical research group is comprised of geriatric psychiatrists and other types of clinical mental health professionals, physical and occupational therapists, a geriatrician, an epidemiologist, an expert in community behavioral health, biostatisticians, and a geropsychologist. Given the complex etiology and natural history of depression and anxiety disorders, a team with expertise in these varied disciplines is needed to guide effective prevention efforts. Unlike other depression prevention work in at-risk older adult populations such as post-stroke[36], macular degeneration[37], and high psychological stress[35] all of which focused on improving problem solving skills, our project compared a behaviorally activating but non-psychological intervention (EXERCISE) with a pain-specific psychosocial intervention (CBT). This type of work, which may have greater generalizability and acceptability by a subsample of our at-risk group, can only be done well with expertise from relevant disciplines.

A lesson learned in this treatment development trial is that older adults with knee arthritis and subsyndromal depression are interested in efforts to maintain their independence and improve their mental health. Engaging patients in an intervention that may both treat a nuisance condition (like pain) but also has mental health-promoting qualities (like CBT and EXERCISE) appears to be an efficient approach to optimizing both physical and mental health. A related lesson learned from this project with relevance for the field of prevention research is where and how participants may be most efficiently recruited. Unlike many of our treatment trials in which we rely heavily of community-based primary care physicians to refer symptomatic patients, in this prevention trial our recruitment succeeded because of direct-to-consumer advertising. Given the challenges of recruitment for all types of studies (both treatment and prevention), effective implementation of recruitment initiatives early on in the trial is critical for achieving recruitment milestones.

Perhaps the greatest limitation to our project is the fact that follow-up is limited to one year. Our study follows participants for a similar length of time as most other prevention protocols. For example, a recent meta-analysis of 32 randomized controlled trials examining the effects of preventive interventions in participants without diagnosed depression described a 21% decrease in incidence over 1–2 years in prevention groups compared to control groups.[38] This is a substantial reduction in incidence, and the field is now poised to

assess participants for longer periods of follow-up. This is important, because in a three year observational study of incident depression, Schoevers et al described that in older adults, subsyndromal symptoms of depression were associated with a risk of almost 40% of developing a depressive episode.[39] Pending the results of this protocol, in our next depression and anxiety prevention program, we plan to monitor participants for at least 3 years.

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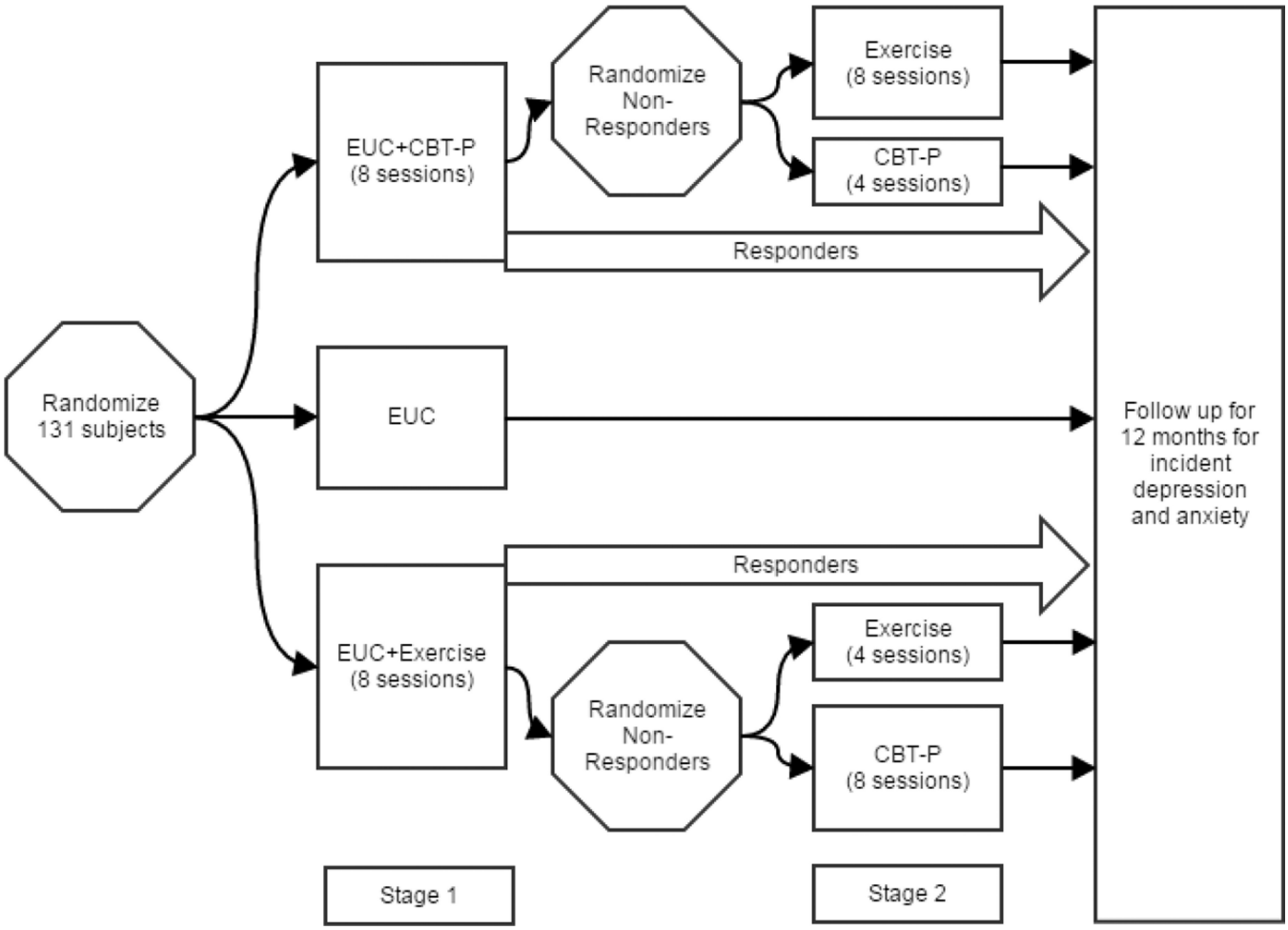

Figure 1.
Study Design
CBT: Cognitive Behavioral Therapy for Pain
EUC: Enhanced Usual Care

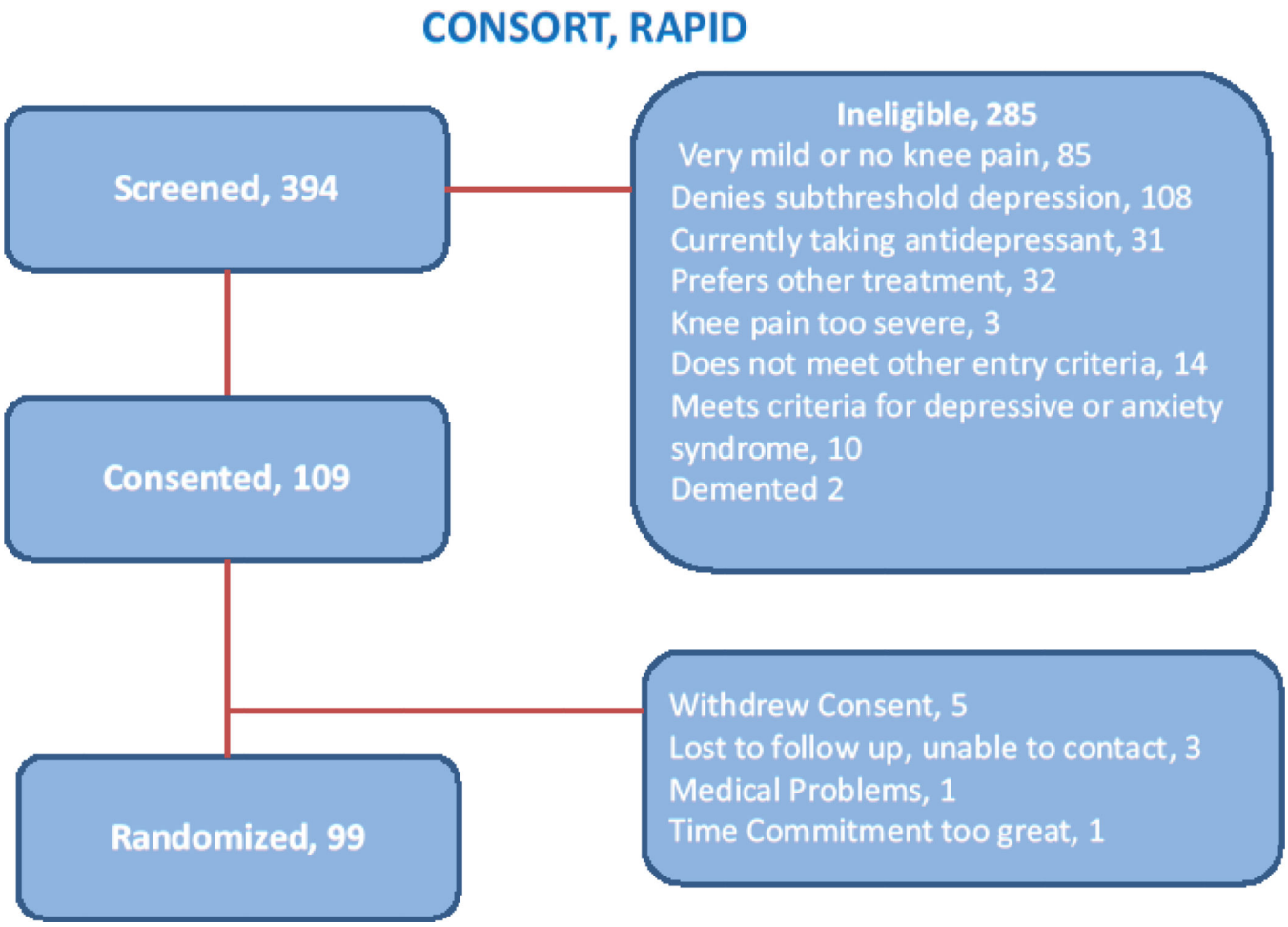

Figure 2.
Consort Diagram

Table 1

Inclusion and Exclusion Criteria and Rationale for These Decisions

Inclusion Criteria	Rationale
≥ age 60	Prevention strategies (i.e., engagement and interventions) for older adults are different than for younger adults
Meets accepted clinical criteria for knee OA based on the American College of Rheumatology 1986 clinical criteria guidelines.[28]	We debated requiring radiographic evidence of knee osteoarthritis, but given that the clinical criteria (knee pain and 3 of the following: > 50 years old, < 30 minutes morning stiffness, crepitus on active motion, bony tenderness, bony enlargement, no palpable warmth of synovium) are what generate distress in patients (not abnormal radiographs), this approach to diagnosis seemed most relevant.
Western Ontario and McMaster University Arthritis Index (WOMAC) pain subscale score in the range of 7–15.	A lower score of 7 includes participants with clinically relevant symptoms of knee OA. For example, a score of 7 could be a patient with either moderate to severe symptoms on one or two items, or someone who may be minimally to moderately impaired on each item. Higher scores suggest either moderate difficulty with all items or severe impairment on several items. Participants with scores > 15 may have symptoms so severe that CBT or EXERCISE may not provide substantial benefit.
PHQ-9 greater than 0, with at least one of the cardinal symptoms of depression (low mood or anhedonia) endorsed.	Indicated prevention trials include individuals who are experiencing early or subthreshold symptoms of the condition of interest. We acknowledge that the majority of older adults with knee OA do not develop MDD or anxiety disorders. However, those with subthreshold depression, along with the knee OA, may be at increased risk of conversion to a syndromal depression or anxiety disorder. Requiring endorsement of depressed mood or anhedonia suggests that these participants may have a diathesis to a mood or anxiety disorder.
Modified Mini Mental State (3MS) Examination ≥>/= 80.[30]	Scores < 80 on the 3MS are highly suggestive of dementia. Scores ≥ 80 include participants with both normal cognition and mild cognitive impairment. To increase generalizability, we wanted to include participants with and without mild cognitive impairment. A prevention trial for individuals with dementia may require a different approach.
Has or is willing to establish care with a personal physician prior to any experimental procedures.	Because participants may be randomized to EXERCISE, which includes aerobic conditioning as part of a home exercise program, for participant safety (in particular cardiac safety), we required permission of their primary care physician for participation.
Exclusion Criteria	
Episode of MDD within the past year.	As this is a study of indicated depression prevention, we did not want to enroll participants currently experiencing a partially treated episode of MDD. The lack of MDD within the past year was established by SCID.
Currently taking an antidepressant	Current use of antidepressant pharmacotherapy could prevent new onset MDD and anxiety disorders above any effect from CBT or EXERCISE.
Currently taking an anti-anxiety medicine > 4 times/week for the past 4 weeks.	Sustained use of anti-anxiety medicine could prevent new onset anxiety disorders.
Lifetime history of bipolar disorder or schizophrenia, or substance use disorder within the past 12 months.	These individuals require treatments beyond the scope of a depression prevention project.
Receiving knee-related workers compensation or involved in knee pain-related litigation.	Individuals involved with these kinds of litigation may experience secondary gain that could interfere with improvement.

Table 2

Baseline and Follow-up Assessments (T1 – T6): Self-report or blinded Independent Assessors

Domain	Measure
Psychiatric Diagnosis	SCID at baseline, MINI/PRIME-MD at every three months in follow-up (Note: The MINI/PRIME-MD is used to assess syndromal depression and anxiety disorders at every follow-up).
Knee Osteoarthritis Diagnosis	American College of Rheumatology clinical criteria for knee osteoarthritis at baseline
Depression severity	Patient Health Questionnare-9 (PHQ-9) *
Anxiety	Generalized Anxiety Disorder-7 (GAD-7) *
Medical burden/Medication Check List/Vitals	Cumulative Illness Rating Scale (CIRS-G) ** Cornell Service Index * Medication List Update * Vitals (Weight, Blood pressure, Hip and Waist Circumference, History of Falls) ** Alcohol Use Disorders Identification Test (AUDIT-C) *
Disability	Late-Life Functional Disability Inventory (LL-FDI) *
Functional status, physical performance	Short Physical Performance Battery (SPPB) **
Insomnia	Pittsburgh Sleep Quality Index (PSQI) *
Overall Body Pain	Numeric Rating Scale for Pain (NRS-20) *
Knee Pain and Disability	Western Ontario and McMaster University Arthritis Index (WOMAC) * Patient Global Assessment of Functioning * Patient Global Assessment of Pain Severity * Catastrophizing Subscale of the Coping Strategies Questionnaire **
Cognitive Status	Repeatable Battery for the Assessment of Neuropsychological Status ** Delis-Kaplan Executive Function System ** Modified Mini Mental State Examination at baseline
Social Isolation/Support	Interpersonal Support Evaluation List *
Problem Solving Skills	Social Problem Solving Inventory (SPSI) **
Biosignatures	Inflammatory Cytokines * (IL6, TNF alpha) + mRNA Transcription (blood draw) * Genetic data only collected at T1
Global Health	Patient Global Impression of Change (PGIC) * RAND-12 * Physical Activity Scale for the Elderly (PASE) *
Satisfaction	5 questions to rate satisfaction plus comment field administered at study Completion

* Baseline and every three months in follow-up

** Baseline and every six months in follow-up

Table 3

Baseline Characteristics (n = 99)

Variable	Descriptive Statistic
Age (years)	71.0 (7.6)
% Female	61.6 (n=61)
% European American	81.8 (n=81)
Education (years)	14.9 (2.6)
Body Mass Index (BMI)	31.7 (8.8)
Cumulative Illness Rating Scale: Total (range = 0–52, higher = worse)	8.6 (3.4)
Cumulative Illness Rating Scale: Count (range = 0–13, higher = worse)	5.6 (2.1)
RAND12 Mental Health Component (t score: mean = 50; SD = 10, higher is better)	47.7 (8.3)
RAND12 Physical Health Component (t score: mean = 50, SD = 10; higher = better)	34.6 (7.3)
Short Physical Performance Battery (range 0–12; higher = better)	9.0 (2.5)
Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale (range 0–20, higher = worse)	9.1 (2.0)
Patient Health Questionnaire (PHQ-9) (range 0–27, higher = more depression)	5.6 (2.1)
Generalized Anxiety Questionnaire (GAD7) (range 0–21; higher = more anxiety)	3.2 (2.7)
Interpersonal Support Evaluation List – modified 12 item (range 0–48; higher = more supports)	40.4 (5.6)

Table 4

Satisfaction Survey Results of 46 Participants Who Exited the Study After 1 Year of Participation.

	Flexibility in scheduling study appointments	Helpfulness of the therapist	Frequency of appointments	Usefulness in managing pain	Usefulness in managing stress
Average score (SD)*	3.9 (0.4)	3.7 (0.5)	3.5 (0.7)	3.2 (1.0)	3.3 (1.0)

** Theoretical range: 1 (highly dissatisfied) – 4 (highly satisfied)

Table 5

Methodological Challenges Experienced During the Study and Solutions

PROBLEM or CHALLENGE	SOLUTION
Subject burden.	**1** Decrease frequency of administration of Short Physical Performance Battery.
10/18/11 Unclear randomization procedure.	**1** Randomization procedure will include stratification history of major depression or an anxiety disorder. **2** The data manager will maintain the randomization list. Once consent is signed, study staff will contact data manager for randomization assignment. **3** Because of the sequenced design, will need to maintain two randomization lists.
Timing of booster sessions	**1** Booster sessions will be administered at 3 and 9 months. **2** Emergency booster sessions are an option and will be documented in the database.
2–10–12 **First participant consented and randomized**.	
Clinical and research management of participants who become syndromal	If a subject develops MDD or anxiety disorder they will exit the intervention but continue in follow-up.
Timing of initiation of follow-up phase	**1** For participants in EUC, theT2 date will be projected for 12 weeks after randomization. **2** For participants receiving interventions, the T2 date may vary and will occur within 1–2 weeks following end of the intervention.
Unclear description about depression symptoms and treatment history at entry into study	**1** Consistent with entry criteria, we will not enroll participants taking antidepressants. **2** Potential participants must endorse either item 1 or 2 on the PHQ9 indicating emotional distress. Without these symptoms endorsed, they may not be at elevated risk for MDD or anxiety disorder.
Assessment of outcomes of interest	**1** The PRIME MD will be done at all assessment timepoints regardless of PHQ & GAD scores to fully evaluate for the onset of a mood or anxiety disorder.
Capture of serious adverse event data. Reminder about anxiety disorders as outcome of interest. Missing items.	**1.** Added a 2 item form to capture hospitalizations that occur during the study. **1.** In addition to MDD, the onset of an anxiety disorder during study participation is considered an end point of the study. This would include any anxiety disorder that would have excluded someone from initial study participation (e.g, generalized anxiety disorder, panic disorder, post traumatic stress disorder). Participants who meet criteria for social anxiety disorder, specific phobias, and anxiety disorder NOS are allowed in the study and these conditions, if they develop during follow-up, would not be considered an endpoint. **1.** When administering the WOMAC, there should not be any missing items. The items should be scored “as if” the person would do the task. For example, if someone only takes showers and the question is “do you have difficulty getting in/out of bathtub”?: ask how much difficulty they would have if they had to get in/out of tub and score accordingly.
Measuring participant engagement	**1** Added a homework Effort/Participation form to capture participant engagement in doing homework between sessions.
Low rates of serial blood draws for biomarkers	**1** To increase rates of blood draws for biomarkers, we will pay for parking and/or a cab to get the blood drawn at the on-site clinic by a trained phlebotomist.
Retention during follow-up	**1** To improve retention during the year of follow-up, we will schedule the next assessment before a participant leaves. We will also send a reminder letter 2–3 weeks before each assessment timepoint and call the subject 2 days before the appointment.

PROBLEM or CHALLENGE	SOLUTION	
Collection of nutritional supplement data.	**1**	All over the counter nutritional supplements will be included on the medication list and entered into the database.
Management of participants who start an antidepressant during participation.	**1**	A subject started on an antidepressant would continue in the study as a regular participant, and they will be eligible for boosters and for scheduled assessments. The data base will reflect exposure to the antidepressant, dose, and medical indication for its having been prescribed.
Emerging concerns about participant burden	**1**	When administering the SCID at baseline, there is no need to administer the somatoform disorders and eating disorders sections.
Management of drop-outs.	**1**	If a subject withdraws from the intervention phases of the study after randomization because they do not like the randomized assignment, we will attempt to complete all assessments over the year of follow-up. If the subject meets criteria for the second randomization and once again refuses the assignment, the plan will still be to complete all assessment time points until the end of the study.
Window of time allowed for collection of follow-up data.	**1**	If a missed visit is more than 6 weeks outside of an assessment time point, we will consider it a missed visit. At the next scheduled assessment, we will just do the assessments required at the current time point. If the final (T6) assessment is difficult to obtain, we can collect this data up to 3 months after the due date to minimize missing data.
Assurance that entry criteria have been met prior to randomization	**1**	To assure participants meet all inclusion and exclusion criteria, the multidisciplinary clinical case review must always be completed prior to randomization.
Further evaluation of alcohol misuse	**1**	To further evaluate alcohol use, we will screen for alcohol with the Alcohol Use Disorders Identification Test (AUDIT- C)[40] will be done on the day of SCID for all participants and this information discussed at the multidisciplinary clinical case review.
Management of delay between screening and baseline.	**1**	If more than 4 weeks lapse between screening and baseline, we must repeat the PHQ9 and Prime MD to assure continued study eligibility.
Management of participants randomized but who never received any intervention.	**1**	Participants who have been randomized but never started their assigned intervention will be considered to be “follow-up only” and every attempt will be made to collect assessments for the following 12 months.