RESEARCH PROTOCOL

Incomplete Response in Late Life Depression: Getting to Remission with Buprenorphine

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1. Synopsis:

Study Title	Incomplete Response in Late Life Depression: Getting to Remission with Buprenorphine
Objective	1) To test the efficacy of buprenorphine (BPN), 2) to examine safety and tolerability of buprenorphine (BPN).
Study Period	Planned enrollment duration: Approximately 3 years Planned study duration: Approximately 28 to 32 weeks per subject
Number of Patients	Enroll approximately 100 participants, aged 50 and older, of both sexes and all races
Study Medication Administration	Subjects will receive an approximate 12 week course of open-label venlafaxine XR. Participants who remit on venlafaxine XR alone will exit the study. Participants meeting criteria for incomplete response will be randomly assigned (2:1) to receive either low-dose buprenorphine or placebo augmentation of venlafaxine for approximately 8 weeks (Phase 2). At the conclusion of Phase 2, all participants can choose to continue into Phase 3. Those that were randomized to placebo in Phase 2 will be offered the chance to receive buprenorphine for approximately 8 weeks. Those that were randomized to the buprenorphine can continue to receive it for Phase 3.
Study Design	A randomized, placebo controlled, double blind parallel group comparison of venlafaxine XR + buprenorphine with venlafaxine XR + placebo for N=20 participants with Treatment Resistant Late Life Depression (TRLLD).
Inclusion and Exclusion Criteria	**Subject inclusion criteria** • Age ≥ to 50 years. • Major depressive disorder (MDD), single or recurrent, as diagnosed by the Structured Clinical Interview for DSM Axis I Disorders (SCID). • Montgomery Asberg Depression Rating Scale (MADRS) ≥ to 15. • Has or agrees to establish a clinical relationship with primary care physician (PCP). • Availability of an informant (e.g., emergency contact). **Subject exclusion criteria** • Inability to provide informed consent. • Depressive symptoms not severe enough (i.e., Montgomery-Asberg Depression Rating Scale (MADRS) < 15) at the baseline assessments). • Dementia, as defined by Modified Mini-Mental State Exam (3MS) < 84 and clinical evidence of dementia (e.g., memory impairment, executive dysfunction, agnosia, apraxia, aphasia, with functional impairment). • Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms, as diagnosed by the Structured Clinical Interview for DSM Axis I Disorders (SCID). • Abuse of or dependence on alcohol or other substances within the past 3 months as determined by Structured Clinical Interview for DSM Axis I Disorders (SCID), and confirmed by study

	physician interview. • Drinking 15 or more drinks per week or consuming 5 or more drinks on any one occasion during the week. • High risk for suicide (e.g., active suicidal ideation (SI) and/or current/recent intent or plan) and unable to be managed safely in the clinical trial (e.g., unwilling to be hospitalized). Urgent psychiatric referral will be made in these cases. • Contraindication to venlafaxine XR or buprenorphine (BPN) as determined by PCP and study physician including history of intolerance of either venlafaxine XR or buprenorphine (BPN) in the study target dosage range (venlafaxine XR at up to 300 mg/day; buprenorphine (BPN) at up to 2 mg/day). • Inability to communicate in English (i.e., interview cannot be conducted without an interpreter; subject largely unable to understand questions and cannot respond in English). • Non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview). • Unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, or cerebrovascular or cardiovascular risk factors that are not under medical management. This will be determined based on information from the patient's personal physician and study physician's clinical judgment. Referral to the patient's personal physician or to a general practitioner will be made in these cases. • Subjects taking psychotropic medications that cannot be safely tapered and discontinued prior to study initiation. The following exceptions are allowed if they have been taken at a stable dose for at least 4 weeks prior to study entry and there is not a plan to change the dose during the next 28 weeks: benzodiazepines up to 2 mg/d lorazepam equivalent; other sedative-hypnotics (e.g., zolpidem, zaleplon, eszopiclone); gabapentin if prescribed for non-psychiatric indication (e.g., neuropathy). • History of opioid abuse or dependence. • Severe pain, defined as $\geq$ 7 on 0-10 numeric rating scale for pain. • Concomitant use of strong or moderate CYP3A4 inhibitor (indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketonazole, nefazodone, saquinovir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem). • Refusal to stop all opioids (to avoid precipitating opioid withdrawal). • Hepatic impairment (AST/ALT > 1.5 times upper normal). • Estimated Glomerular Filtration Rate (GFR) < 20 ml/min. • Inability/refusal to identify a person as an emergency contact. • Pregnancy • Failure to meet inclusion criteria for imaging sub-study
Measurements	Pharmacogenetic collection, NIMH genetic sample and Safety Labs (CMP and CBC w/ diff), urine test, and EKG will be obtained at baseline. All participants randomized will have biomarker collections done at the beginning and end of Phase 2. Venlafaxine levels will be collected at the end of Phase 1. Buprenorphine levels will be collected at the beginning and

	end of Phase 2. Depression outcomes measured using the Montgomery-Asberg Depression Rating Scale (MADRS). Drug side-effects assessed with the Antidepressant Side-Effect Checklist (ASEC) and Frequency, Intensity, and Burden of Side Effects Rating (FIBSER).
Statistical Methodology	Our planned primary dichotomous outcomes are (1) remission rate (2) rate of serious adverse events, while our planned continuous outcomes are (1) Montgomery-Asberg Depression Rating Scale (MADRS) scores (2) side effect rating changes. These analyses will be combined with other, secondary clinical outcome analyses of scales to address the primary question of whether there appears to be an efficacious and safe dose of buprenorphine (BPN) for LLD. For each such analysis, both main effects and treatment interaction term will be examined. Simple log-rank tests and Cox proportional hazard models will be the primary analytic approaches to compare time to remission among groups. If the number of remissions is small, then exact tests of proportions will be performed. Analyses will be conducted using the intent to treat (ITT) principle. We will examine dropout attributable to adverse events, utilizing data from Phase 2, with survival analysis (with censoring at time of dropout or removal from the study). This will include dropout due to patient decision as well as due to clinical decision. Mixed-effect models will be used to examine repeated Montgomery-Asberg Depression Rating Scale (MADRS) scores.

2. Study Protocol:

2.1 Background and Significance

Late-life treatment resistant depression (LL-TRD) is a large public health challenge: at least 50% of older people fail to respond adequately to antidepressant pharmacotherapy. Getting to and sustaining remission is the primary goal of treatment, yet there is a paucity of controlled studies of how best to manage LL-TRD. The development and testing of novel-mechanism pharmacotherapies is a public health priority embraced by NIMH. Table 1 lists some of the most devastating consequences of LL-TRD.

LL-TRD is a common and potentially devastating condition, yet we have an extremely limited evidence basis for its management: clinicians do not have data to guide them regarding which augmentation agent to use, in whom, how, or with which risk/benefit ratio. This study will be the first placebo-controlled trial to examine a modern pharmacologic treatment for LL-TRD. If our hypotheses are supported, this study will establish a new approach to LL-TRD. It will also lead to a greater understanding of reasons for observed treatment resistance and thus ultimately to personalized treatment for LLD.

Table 1. Consequences of LL-TRD
Suicide
Cardiac morbidity
Hastened cognitive decline
Worsened diabetes
Worsened pain
Higher caregiver burden
Higher all-cause mortality

Almost no data exists to guide the treatment of LL-TRD. The only published placebo-controlled pharmacotherapy trial for LL-TRD found that the monoamine oxidase inhibitor (MAOI) selegiline was efficacious. However, in a recent randomized comparison of lithium augmentation and the MAOI phenelzine for LL-TRD, one-third of those receiving lithium remitted versus none receiving phenelzine; these two controlled studies suffer from small sample size, short duration, and inclusion of subjects with psychosis. Our research group has open pilot data from 15 older adults with treatment-resistant depression who received low-dose buprenorphine (BPN). (See Section 2.3)

2.2 Objective

The overall purpose is to examine the feasibility, safety, and tolerability of low-dose buprenorphine (BPN) as a novel treatment for late-life treatment resistant depression (LL-TRD) while also determining optimal dosing strategies to improve acceptability.

Among the neuropeptidergic transmitters, opioids are known to modulate mood, and this system is often altered in patients with major depression. Targeting the opiate system in LL-TRD may positively modulate a system in which there is age-associated imbalance. [1-4] Buprenorphine (BPN) is an antagonist at the kappa opiate receptor and a partial agonist at the mu opiate receptor. Either, or both, of these pharmacodynamic actions may underlie its putative antidepressant effects. In addition, since buprenorphine (BPN): 1) is available in sublingual formulation and 2) has a favorable safety and pharmacokinetic profile; it is an attractive candidate to use for LL-TRD. Thus, the overarching aims of this project are to examine the feasibility, safety, tolerability and clinical effect of low-dose buprenorphine (BPN) as a novel treatment for LL-TRD.

2.3 Approach: Preliminary Studies

2.3.1 The opiate system modulates mood, reward behavior, and well-being.

As mentioned above, among the neuropeptidergic transmitters, opioids are known to modulate mood. Opiate receptors and endorphins are highly concentrated in the limbic and hypothalamic regions and interact with the monoaminergic system.[5] Numerous studies have shown that opiate receptor neurotransmission is altered in patients diagnosed with major depressive disorder.[6-9] Other studies have shown that when morphine is injected directly into the dorsal raphe nucleus, there is suppression of GABAergic-mediated inhibition of serotonin release.[10] This results in a disinhibition of serotonergic neurons and the release of excess central 5-HT in forebrain projection areas related with emotional integration, including the thalamus, nucleus accumbens, amygdala, frontal cortex, striatum, hypothalamus and ventral hippocampus.[11]

Buprenorphine (BPN) is an antagonist at the kappa-OR and a partial agonist at the mu-OR; considerable evidence supports either, or both, of these pharmacodynamic actions as underlying the antidepressant effects of buprenorphine (BPN). There is accumulating evidence that antagonism of the kappa-OR produces an antidepressant effect. Antagonism of kappa-OR may produce an increase in monoaminergic signaling pathways, producing a functionally similar response to monoaminergic reuptake inhibitors. However, it has also been observed for centuries that agonism of the μ-OR (e.g., “the opium cure”)[12] leads to feelings of well-being and anxiolysis.[13,14] Given the feasibility and treatment development nature of this project, we will focus on both mu-OR and kappa-OR mechanisms in this study. We acknowledge that the delta-OR may have effects on mood[15], but given the early phase of our work, we will focus on the two opiate receptor subtypes with the greatest support in the literature.

2.3.2 Age-Related Changes in the Opiate System Support Our Focus on LL-TRD.

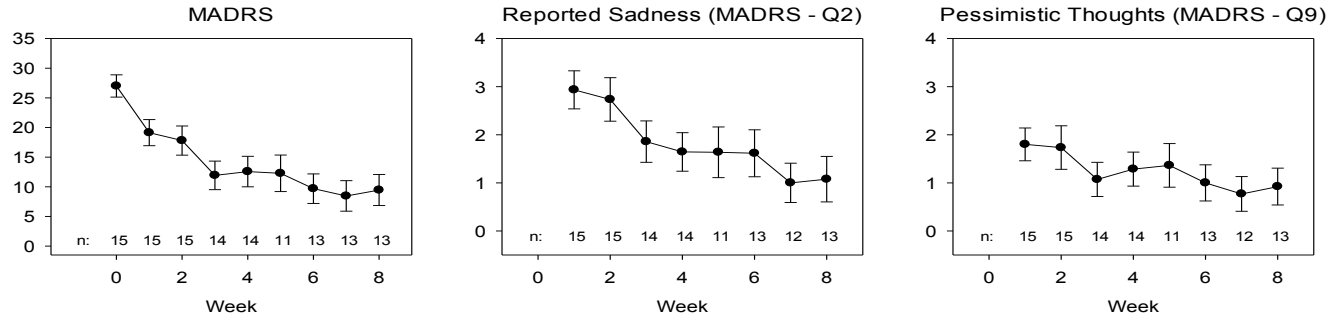
While there is variability in the animal and human evidence supporting age-related changes in the opiate system, the human studies suggest age-associated increases in density and binding affinity for mu-OR. The majority of the animal aging studies indicate increased density and binding affinity for kappa-OR, in particular in the thalamus and amygdala. Increased density and binding affinity are consistent with work suggesting age-related decrease in endogenous opiates such as enkephalin and endorphin.[16,17] Targeting the opiate receptor system in LL-TRD may alter a system in which there is imbalance between circulating opiates and the density and affinity of mu-OR and kappa-OR.

2.3.3 Buprenorphine is poised to be repurposed for treating LL-TRD. Novel agents with unique mechanism of action and rapid onset require study when monoaminergic antidepressants are ineffective. Testing the efficacy and probing the mechanism of unique molecules is a focus of both personalized care and translational bench-to-bedside research, two priority aims of the NIMH strategic plan.[18] As outlined in the NIMH Council monograph “From Discovery to Cure,” psychiatry must catch up with other fields of medicine,

such as cardiology, in the identification and testing of therapeutics that are mechanistically distinct. In view of the general decline of psychiatric drug development by "big pharma"[19], our repurposing of buprenorphine (BPN) (i.e., the application of buprenorphine for the different indication[20] of LL-TRD) responds to this need.

2.3.4 Buprenorphine may rapidly improve LL-TRD: We recently completed an 8 week open-label clinical trial (n=15) using low dose buprenorphine (BPN) for LL-TRD patients (50 and older).[21] The average age of these subjects was 60.7 (SD 5.6); 53.3% were female. Twelve of the subjects received buprenorphine (BPN) as augmentation pharmacotherapy (vs. as monotherapy for 3). The most commonly co-prescribed antidepressants were venlafaxine, citalopram, and duloxetine.

Figure 1. Change in the Total MADRS Score and Depression-Specific Items During Open Exposure to BPN



MADRS: Montgomery Asberg Depression Rating Scale

The average daily dose of buprenorphine (BPN) was 0.6 mg/day. The Montgomery-Asberg Depression Rating Scale (MADRS) improved from average score of 27.0 (7.3) at baseline to 9.5 (9.5) at week 8, Cohen's d=1.9 (figure 1). We observed the same magnitude of decrease in the depressed mood and pessimistic thoughts items, supporting benefits for core depressive symptoms. The overall remission rate was 60% based on criteria of Montgomery-Asberg Depression Rating Scale (MADRS)$\leq$10 at week 8. Weight and vital signs remained stable. Although these data are from a relatively young TRD sample, stratification by age (based on a median age split of 62.5 years) revealed no difference between the "younger" and "older" groups." The subject who was 62.5 is included in the older group, since the groups are then < 60 and $\geq$ 60. Response rates (defined as MADRS < 10 at week 8) for the younger group was 83.3% (n=5/6) and 42.9 (n=3/7) for the older group (Fisher exact p = 0.27).

Reasons for early termination included: 1) constipation and bloating (n=1) and 2) two subjects were removed from the study because of worsened pre-existing chronic suicidality (exacerbations directly linked with psychosocial stressors). In addition to core depressive symptoms, participants also improved in anxiety (BSI anxiety subscale at baseline = 1.1 (0.7), week 8 = 0.6 (0.8)), sleep (PSQI at baseline = 9.9 (3.5), week 8 = 6.0 (2.8)) and the positive affect subscale of the PANAS (baseline = 21.5 (8.6), week 8 = 29.4 (12.0)). However, at week 16 (8 weeks after discontinuation of the buprenorphine (BPN)), the average MADRS score was 17.8 (12.9; range=2-39), suggesting that buprenorphine (BPN) must be maintained long-term for continued antidepressant effect. Of note, 3 subjects sought continued treatment with buprenorphine (BPN) to maintain depression remission after completing the protocol. We also preliminarily examined buprenorphine (BPN)'s safety. Improvements in memory and executive function (assessed with the Hopkins Verbal Learning Test and a computerized test of attention) from baseline to week 8 support the safety on cognition of buprenorphine (BPN) in this population. We did not observe any symptoms of opiate withdrawal or craving, measured with the Clinical Opiate Withdrawal Scale (COWS),[16] following the tapered discontinuation of buprenorphine (BPN). Further safety evaluation of buprenorphine (BPN) is a key component of this proposal and provides a rationale

for the neuropsychological testing. In summary, this project indicates our success at recruiting and retaining very ill, treatment resistant patients into a protocol using buprenorphine (BPN).

2.4 Patient Selection

We will enroll approximately 100 participants, aged 50 and older, of both sexes and all races. Participation may last approximately 32 weeks. Previous participants in the "Incomplete Response in Late Life Depression: Getting to Remission", ("IRL Grey") multi-site R01, 201101816, who did not remit will be asked to participate. Other participants will be recruited with the assistance of recruitment strategies utilized in previous studies (VFH, HealthStreet, PCP referrals…). Subjects will be screened with the Structured Clinical Interview for DSM Axis I Disorders (SCID) to determine eligibility.[9] Structured Clinical Interview for DSM Axis I Disorders (SCID) assesses current and lifetime depression, as well as other psychiatric disorders, and is used to clarify psychiatric inclusion and exclusion criteria. Participants must have current Major Depressive Disorder (MDD). All risks and benefits will be explained, and subjects will sign an informed consent form. We will screen for ETOH abuse and dependence (using the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) and substance abuse and dependence section of the Structured Clinical Interview for DSM Axis I Disorders (SCID)). We will exclude anyone with evidence of active ETOH or substance abuse. We will utilize a clinical trial that has 3 Phases. In Phase 1 we will treat all participants with an approximate 12 week course of open-label venlafaxine XR. This is the same lead-in treatment as in our ongoing "IRL Grey" multi-site R01 for LL-TRD, and we have found it to be highly successful. Participants who remit on venlafaxine XR alone will exit the study.

Phase 2, RCT Overview: In the approximate 8-weeks of buprenorphine (BPN) vs. placebo, twenty subjects will be randomized (using permuted block randomization) 2:1 to receive venlafaxine XR (at the dose they reached and tolerated in the open-label lead-in) plus either buprenorphine (BPN) or placebo. The reasons for using a 2:1 random allocation include: 1) collection of data about plasma levels of buprenorphine (BPN), and 2) gaining further clinical experience with the molecule. Both of these reasons are consistent with the developmental nature of the R34 grant mechanism (the NIH grant mechanisms supporting this project). We will use independent evaluators (who are blind to treatment assignment) at the end of Phase 2 for the last two assessments to determine if the participant has met response. The reason for using independent evaluators at this pivotal time point is that clinicians may become unblinded because they are also assessing side effects. Additionally, we will collect buprenorphine (BPN) plasma levels on all those randomized to explore a dose-effect relationship on treatment response. The study will be posted on clinicaltrials.gov, once reviewed and approved by the Institutional Review Board (IRB).

At the conclusion of Phase 2, the blind will be broken for all participants.

Participants will undergo 2 MRI's in Phase 2, unless it is unsafe for them to do so.

Neuroimaging: MRI

The first MRI will take place before the administration of buprenorphine or placebo. The second scan will occur at approximately week 8 after the administration of buprenorphine or placebo. Scans will be performed at the CCIR. The imaging protocol includes the following sequences: 1. Structural T1-weighted and T-2 weighted lasting ~6 minutes each 2. Practice of behavioral task to record participant's reaction time lasting 5 minutes 3. Two resting state scans ~5 minutes each 4.BOLD image during performance of the behavioral task lasting 22 minutes (approximately 5- runs). The total scan time will be about 1 hour. Subjects will be asked to lie still during the scan. At the end of the task and outside the scanner subjects will undergo emotional ratings about how they felt while doing the task in each of the three types of trials this will take about 5 minutes. During each MRI subjects will perform the Monetary Incentive Delayed task (MID) developed by Knutson et al (Neuroimage 2000, 12: 20-27). This task is designed to elicit neural responses to monetary incentive anticipation and outcomes. This task activates brain regions including striatal and mesial forebrain structures (including insula, caudate, putamen, and mesial prefrontal cortex) during trials involving reward and punishment. It has been recently validated by NIMH-funded research as an fMRI task to measure functional opioidergic effects of KOR antagonists.

This task has three kinds of trials: reward, neutral and loss trials (punishment). For reward trials subjects will be able to earn between $1.50 and $2.40 if they respond fast enough, for neutral trials the will not gain or lose any money and for loss trials, they will lose between $1.80 and $2.20 if they respond too slowly.

At the onset of each trial subjects are presented with a visual cue (1.5 seconds) indicating a reinforcer associated with performance "+ $" for reward, "0 $" for neutral and "- $" for loss trials. After a variable inter-stimulus interval (3, 4.5 or 6 seconds) participants will see a visual target (a red square, 0.2 seconds) signaling they should press a button (on a key pad they hold on their hand) as quickly as possible. After they respond, visual feedback will be provided regarding gains, no change (for neutral trials) or losses; however no information about overall performance will be provided during performance of the task. Prior to start the task subjects undergo practice inside the scanner to record their reaction times. In this task gains are associated with successful performance in reward trials occurring when the participant's reaction time (after they see the red square) is within the 70th percentile of those obtained in the previous run (for run 1, the practice run is used for this calculation).

Once the participant has finished the scan, study staff will provide feedback about how they did on the task and indicate how much they will receive. Subjects may receive up to $50 dollars cash for performing the task. Based on experience using this task in depressed subjects provided by other investigators and based on calculations of the maximum wins and the maximum losses adjusted by the 70th percentile reaction time, we have determined to give a set amount of money close and up to $50 to each participant at the end of the task which will be assigned in a counterbalanced order

Phase 3, open-label buprenorphine (BPN) plus venlafaxine: We aim to collect data on the durability of clinical effect of buprenorphine (BPN). All participants, regardless of their treatment assignment or response in Phase 2, can participate in Phase 3. Those who had received BPN will continue to receive it, with further up-titration of the dose (maximum 1.2mg/d) as needed and tolerated. Those who had received placebo in Phase 2 will start at 0.2mg/d with up-titration a needed and tolerated. This Phase will last approximately 8 weeks for all participants. We will carry out clinical ratings at each visit in order to follow symptoms and side effects of treatment. The Phase 3 variations will allow all participants a chance to experience the benefits of BPN. Efficacy and tolerability data will provide a clinically informative estimate of benefits and risks of BPN augmentation for LL-TRD.

2.5. Inclusion Criteria

Subject inclusion criteria

- Age ≥ to 50 years.
- Major depressive disorder (MDD), single or recurrent, as diagnosed by the Structured Clinical Interview for DSM Axis I Disorders (SCID).
- Montgomery Asberg Depression Rating Scale (MADRS) ≥ to 15.
- Has or agrees to establish a clinical relationship with primary care physician (PCP).
- Availability of an informant (e.g., emergency contact).

Subject exclusion criteria

- Inability to provide informed consent.
- Depressive symptoms not severe enough (i.e., Montgomery-Asberg Depression Rating Scale (MADRS < 15) at the baseline assessments
- Dementia, as defined by 3MS < 80 and clinical evidence of dementia (e.g., memory impairment, executive dysfunction, agnosia, apraxia, aphasia, with functional impairment).
- Lifetime diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms, as diagnosed by the Structured Clinical Interview for DSM Axis I Disorders (SCID).

- Abuse of or dependence on alcohol or other substances within the past 3 months as determined by Structured Clinical Interview for DSM Axis I Disorders (SCID), and confirmed by study physician interview.
- Drinking 15 or more drinks per week or consuming 5 or more drinks on any one occasion during the past week.
- High risk for suicide (e.g., active suicidal ideation (SI) and/or current/recent intent or plan) and unable to be managed safely in the clinical trial (e.g., unwilling to be hospitalized). Urgent psychiatric referral will be made in these cases.
- Contraindication to venlafaxine XR or buprenorphine (BPN) as determined by PCP and study physician including history of intolerance of either venlafaxine XR or buprenorphine (BPN) in the study target dosage range (venlafaxine XR at up to 300 mg/day; buprenorphine (BPN) at up to 2 mg/day).
- Inability to communicate in English (i.e., interview cannot be conducted without an interpreter; subject largely unable to understand questions and cannot respond in English).
- Non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview).
- Unstable medical illness, including delirium, uncontrolled diabetes mellitus, hypertension, or cerebrovascular or cardiovascular risk factors that are not under medical management. This will be determined based on information from the patient's personal physician and study physician's clinical judgment. Referral to the patient's personal physician or to a general practitioner will be made in these cases.
- Subjects taking psychotropic medications that cannot be safely tapered and discontinued prior to study initiation. The following exceptions are allowed if they have been taken at a stable dose for at least 4 weeks prior to study entry and there is not a plan to change the dose during the next 28 weeks: benzodiazepines up to 2 mg/d lorazepam equivalent; other sedative-hypnotics (e.g., zolpidem, zaleplon, eszopiclone); gabapentin if prescribed for non-psychiatric indication (e.g., neuropathy).
- History of opioid abuse or dependence.
- Severe pain, defined as $\geq$ 7 on 0-10 numeric rating scale for pain.
- Concomitant use of strong or moderate CYP3A4 inhibitor (indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketonazole, nefazodone, saquinovir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem).
- Refusal to stop all opioids (to avoid precipitating opioid withdrawal).
- Hepatic impairment (AST/ALT > 1.5 times upper normal).
- Estimated Glomerular Filtration Rate (GFR) < 20 ml/min.
- Inability/refusal to identify a person as an emergency contact.
- Pregnancy

2.6 Design and Procedures

2.6.1 Study Design

The protocol is a randomized, placebo controlled, double blind parallel group comparison of venlafaxine XR + buprenorphine with venlafaxine XR + placebo for N=20 participants with Treatment Resistant Late Life Depression (TRLLD). Subjects will be studied for approximately 32 weeks: an approximate 12-16 week lead-in phase of open-label venlafaxine XR, an approximate 8 week RCT of buprenorphine (BPN) vs. placebo as an augmentation to venlafaxine XR, and approximately 8 weeks open-label buprenorphine (BPN) plus venlafaxine phase. Following the informative design of IRL GREY, participants will be aged 50 years and older, with MDD and a MADRS score $\geq$ 15; they will be primarily recruited from previous studies. The goal of treatment is remission, defined as a MADRS $\leq$ 10 for at least two consecutive assessments.

2.6.2 Open-label lead-in with venlafaxine XR: We will prospectively determine treatment resistance by initially treating participants with a 12-16 week course of open-label venlafaxine XR (figure below).

Approximately 100 participants will start venlafaxine XR 37.5 mg daily and will rapidly (2 weeks) titrate to 150 mg/d. Then, at week 6, those who inadequately respond to this dose will have venlafaxine titrated (as tolerated) further, up to a maximum dose of 300 mg/day. At the end of 12 weeks, those who achieve remission (Montgomery-Asberg Depression Rating Scale (MADRS) $\leq$ 10 for 2 consecutive assessments) with venlafaxine will exit the study; non-remitters will be eligible for the RCT of buprenorphine (BPN) vs. placebo augmentation. Visits and assessments during open-label lead-in are weekly for the first two weeks and then every other week.
We have experience using this titration schedule for the 3-site IRL GREY clinical trial; our experience suggests this titration schedule optimally balances efficacy, safety, and tolerability. The attrition rate for this study because of intolerable side effects is < 4% by week 12. This design confers the advantage of prospectively showing treatment resistance, instead of relying on historical data (which may be unreliable).

2.6.3 Rationale for use of venlafaxine XR: Prior studies by our research team and published guidelines have suggested that a switch to an SNRI is reasonable for LLD patients who do not respond to an SSRI.[22-24] We also chose venlafaxine XR as the sole agent for the open-label lead-in because: 1) it is approved for treating depression; 2) it lacks drug-drug interactions (including with buprenorphine (BPN)); 3) there is evidence for its use in older persons; and 4) we have successfully used this medication in prior studies of LLD and LL-TRD[23,25] and in an ongoing trial across 3 sites.[26] In addition, venlafaxine acts as an SSRI at lower doses and an SNRI at higher doses.[27,28] Thus, based on our team's experience, and published recommendations[29], an initial 6-week period at 150 mg/d, followed by a second 6-week period at 300 mg/d, appears optimal in attaining remission with venlafaxine with the minimum likelihood of adverse effects and is, in a sense, two 6-week medication trials: one with low-dose venlafaxine as an SSRI, and one with high-dose venlafaxine as an SNRI. The primary reason for continuing venlafaxine during phase 2, even though subjects will be considered to be non-remitters, is to leverage any clinical improvements gained during phase 1. Since the antidepressant effect of buprenorphine (BPN) is not established, it would be unethical to withdraw the venlafaxine in older patients with TRD who might have experienced some benefit from it. Even if there is no evidence of an antidepressant effect, there may be other benefits (e.g., reduced anxiety and anger, decreased suicidal ideation, improved sense of well-being) in which subjects may benefit from continued exposure to the medication. Finally, adding buprenorphine (BPN) to the venlafaxine supports our testing of buprenorphine (BPN) as an augmentation agent.

2.6.4 RCT Overview:
Phase 2, RCT Overview: In the approximate 8-weeks of buprenorphine (BPN) vs. placebo, twenty subjects will be randomized (using permuted block randomization) 2:1 to receive venlafaxine XR (at the dose they reached and tolerated in the open-label lead-in) plus either buprenorphine (BPN) or placebo. The reasons for using a 2:1 random allocation include: 1) collection of more data about plasma levels of buprenorphine (BPN), and 2) gaining further clinical experience with the molecule. Both of these reasons are consistent with the developmental nature of the R34 grant mechanism (the NIH grant mechanisms supporting this project). We will use independent evaluators (who are blind to treatment assignment) at the end of phase 2 for the last two assessments to determine if the participant has met response. The reason for using independent evaluators at this pivotal time point is that clinicians may become unblinded because they are also assessing side effects.

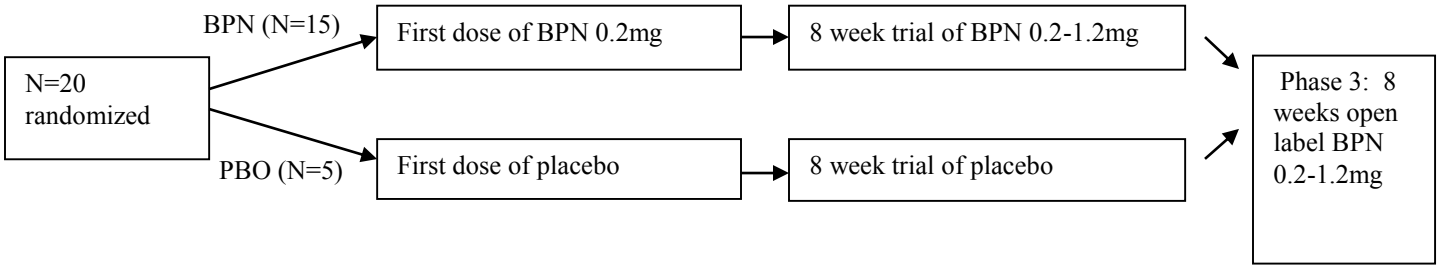
2.6.5 Titration schedule of buprenorphine (BPN): buprenorphine (BPN) will be started at 0.2 mg/d and will be titrated weekly by 0.2 mg, based on tolerability (assessed with the FIBSER) and depression severity (assessed with Montgomery-Asberg Depression Rating Scale (MADRS). The minimum target dose is 0.6 mg/d (based on our pilot work) with an allowed maximum of 1.2 mg/d. The primary outcome will be remission at the end of the Phase 2.

Since the analgesic effects of buprenorphine (BPN) may obscure the antidepressant effects, we will exclude subjects with severe pain. This will be defined as a score of > 7 on a 0-10 Numeric Rating Scale for Pain. The time assessed for pain will be the previous month (note: we are not trying to diagnose a chronic pain syndrome, but exclude those with recent clinically significant pain). We have decided to not exclude all

individuals who endorse pain, since they represent the majority of older adults with depression. Therefore, we will include pain levels < 7.

Consistent with the developmental aim to learn more about dosing ranges and plasma levels, we will extend Phase 2 to approximately eight weeks with a maximum dose of 1.2 mg/d. This is a complicated dosing regimen (with up to a 6-fold variability of doses). With this approach, we expect to clarify the range of efficacious and tolerable doses for buprenorphine (BPN), ultimately resulting in a more parsimonious dose titration schedule. This is of great importance, as the appropriate dose range is not yet established. In order to ensure that subjects do not experience withdrawal, we will taper the study drug at the end of the study for all participants. The study drug will be tapered by 20% every 3 days until discontinued. We will use the Clinical Opiate Withdrawal Scale (COWS) to assess any symptoms of withdrawal and adjust the discontinuation as needed to assure a comfortable discontinuation for subjects. In our pilot work, we have not encountered ANY discontinuation symptoms during the cessation of buprenorphine (BPN).

2.6.6 Open label buprenorphine (BPN) plus venlafaxine XR:
Phase 3, Assessing durability of clinical response: While a relapse prevention study would require a different design, we aim to collect data on the durability of clinical effect. The blind will be broken for all participants at the end of Phase 2. All are welcome to continue into Phase 3 of the study. Phase 3 allows those who did not receive BPN a chance to titrate to the highest, most beneficial dose offered through this clinical trial. Those who did receive BPN but did not reach remission are offered an additional 8 weeks to titrate to a higher dose, possible more beneficial dose as tolerated. And those who did receive BPN and found it beneficial are offered 8 more weeks at this remission dose. At the end of Phase 3, BPN will be tapered as described above.



2.7 Assessments:

2.7.1 Assessments and Primary Outcomes

Subjects will be evaluated with the following measures:

Structured Clinical Interview for DSM-IV (or DSM-5, depending on when the new DSM is published) disorders (SCID). The SCID will involve the collection of information from the consenting individual alone. We will not require an outside source to provide information or validate information supplied by the consenting individual.

The Montgomery-Asberg Depression Rating Scale (MADRS) will be our main depression outcome measure. A MADRS score >15 at baseline will establish study eligibility.

Comorbid physical illness will be measured with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), which we have validated and frequently used to quantify total medical burden.

Documentation of Previous Treatment Resistance: Treatment history will be assessed with the Antidepressant Treatment History Form (ATHF) to further characterize the sample.

Since pain of various etiologies is highly prevalent in late-life has been shown to moderate treatment outcome and may be improved with buprenorphine (BPN), we will assess pain with a Numeric Scale of 0-10 (NRS-P).

Sleep quality is a critical covariate of depression onset and response. We will assess sleep quality with the Insomnia Severity Index (ISI).

To address the aim of tolerability and safety, we will assess vital signs and weight at approximately every visit.

The experience of euphoria (or a feeling of being "high") will be assessed with two 0-10 visual analog scales.

Side effects will be assessed with the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) and the Antidepressant Side Effect Checklist (ASEC) at every visit.

Symptoms of withdrawal after study medication taper and discontinuation will be assessed with the Clinical Opiate Withdrawal Scale (COWS).

Scale for Suicide Ideation (SSI). It has been shown to predict completed suicide [30,31] and has moderately high internal consistency with Cronbach's alphas ranging from 0.84 to 0.89 and good inter-rater reliability [32,33]. To reduce participant burden, 5 screening items are administered; if any are endorsed, the participant completes items 6-19. The full SSI takes 10 minutes to administer. For every enrolled participant, we also utilize a checklist of suicide risk and suicide protective factors.

Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)[34]: The theoretical range of scores for the AUDIT-C is 12. Patients who report drinking 4 or more (women) or 5 or more (men) drinks in a day during the interval period on the single-item screening question are considered to have unhealthy use of alcohol. If subjects have an AUDIT-C score > 8, we will evaluate them with the substance use disorder section of the Structured Clinical Interview for DSM Axis I Disorders (SCID) to further refine their clinical state and to help us decide if it is safe for them to remain in the study and/or if they require referral for specialty alcohol use treatment.

Brief Symptom Inventory (BSI-anxiety) will be used to measure general anxiety symptoms. We have reported that the BSI-anxiety scale has good internal consistency in LLD subjects (Cronbach's alpha = 0.84) and a score >1.0 predicts decreased response in LLD and increased recurrence rate during maintenance treatment. It will be our primary outcome measure of anxiety because of its low burden and our group's experience with it.

Patient Global Impression of Change (P-GIC) will also be utilized. This self-report scale is used to measure a subject's individual perception of change or no change in terms of how they are feeling.

Adherence Form will be administered at every visit (with the exception of screening/ baseline) to monitor medication adherence as well as alcohol and substance use.

Suicide History Form will be administered once at screening/ baseline to gather historical suicidal thoughts and behaviors. We will not require an outside source to provide information or validate information supplied by the consenting individual.

2.7.2 Neuropsychological functioning will be assessed with the following:
3MS (Modified Mini-Mental State Exam). This cognitive screening test, which is an expanded version of the Mini-Mental Status Exam, has a score range of 0-100. In addition to providing a broader variety of cognitive functioning and a wider range of difficulty, the original MMSE score can be extracted. A score of at least 80 is required to enter the study, as scores below this may indicate dementia.

Trail Making Test (parts A & B) (Halstead, 1947). Part A consists of 25 circles numbered 1 through 25

distributed over a page. The subject is instructed to connect the circles with a pencil line as quickly as possible in ascending numerical order. Part B also consists of 25 circles, but these circles contain numbers (1 through 13) or letters (A through L). The subject must connect the circles while alternating between numbers and letters in ascending order. The subject's performance is based on the time required to complete each part and by the number of errors. Both parts A and B require visuomotor and perceptual scanning skills, but part B also requires flexibility in shifting from number to letter sets while under time pressure.

Hopkins Verbal Learning Test- Revised (Brandt & Benedict, 2001). The HVLT-R offers six alternate forms. Each form contains 12 nouns, four words each from one of three semantic categories (e.g., precious gems, articles of clothing, vegetables, etc.), to be learned over the course of three learning trials. Approximately 20-25 min later, a delayed recall trial and a recognition trial are completed. The delayed recall requires free recall of any words remembered. The recognition trial is composed of 24 words, including the 12 target words and 12 false-positives, 6 semantically related, and 6 semantically unrelated. This is a test of verbal learning and episodic memory.

Letter-Number Sequencing from the WAIS-4 (Wechsler, 2008). Examiner presents combinations of letters and numbers, from 2 to 9 letter-number combinations. Examinee must repeat each series by first repeating the numbers in ascending order, then the letters in alphabetical order (e.g., 9-L-2-A; correct response is 2-9-A-L). This task measures "working memory," the ability to simultaneously recall and organize stimuli of different, similar types.

Nebes' computerized Reaction Time Tasks (Jennings et al., 2011). These two computerized tasks with repeatable conditions measure basic attention, psychomotor speed, and inhibition. The tasks include a Choice Reaction Time Task and a Congruous vs. Incongruous Conditions Reaction Time Task. The simple Choice Reaction Time Task involves pressing a button held in the dominant hand as soon as a 1 cm dot appears in the center of the computer screen. The interstimulus interval is preset and varies randomly between 1.5 and 3 seconds so that the participant cannot anticipate stimulus onset.

The Congruous vs. Incongruous Conditions Reaction Time Task, consists of trials in which a right- or left-pointing arrow appears 8.5 cm to the right or left of the central fixation. The participant is instructed to press the button on the side toward which the arrow pointed. There were two conditions: Congruous and Incongruous. In the Congruous condition, the spatial location of the arrow (i.e., the side of the screen on which it appeared) is the same as the direction the arrow is pointing (e.g., a left-pointing arrow appears to the left of fixation). In the Incongruous condition, the location of the arrow conflicts with the direction in which it is pointing (e.g., a right pointing arrow appears to the left of fixation). In this condition, the participant has to inhibit processing the arrow's location, focusing only on the direction it is pointing. There are 40 congruous and 40 incongruous trials randomly intermixed. Prior to this experimental block, a block of unscored trials reinforced the prepotent spatial response: subjects respond to a rectangle on the left or right of the screen on the spatially congruent key.

Computerized Reward Response Task (Pechtel, 2013): This probabilistic reward task (PRT), uses a differential reinforcement schedule of monetary feedback to examine reward responsiveness. The task uses monetary incentives (“Correct! You won 5 cents”) as reward feedback. The 15-20 min task is presented on a 1700 PC monitor using E-Prime software (Version 1.1.; Psychology Software Tools Inc., Pittsburgh, Pennsylvania). Participants complete three blocks of 100 trials (monetary reward) to induce a response bias towards the more frequently rewarded stimulus (RICH) compared to the less frequent rewarded stimulus (LEAN). Reward feedback is provided three times more often for the RICH than the LEAN stimulus. Participants are instructed that the goal of the task was to win as much money as possible and are informed that not every correct response will lead to a reward feedback. In each block, a pseudo-random sequence of 50% long and 50% short mouths are presented. Each trial consisted of a fixation cross (jittered 750-900 ms) followed by a mouth-less line drawing of a face (500 ms), after which either a short (11.5 mm) or a long (13 mm) mouth appears on the face (100 ms). Participants are instructed to press one of two keyboard keys to indicate whether the mouth was long or short. Reward feedback is displayed on the computer screen (1500 ms). Keys and conditions (long

or short mouth as RICH stimulus) are counterbalanced across participants. Participants complete a short series of practice trials to ensure they understand the instructions.

3. Data Collection, Management, and Analysis:

Before major analyses, we will examine all variables descriptively using cross-tabulations, histograms, and tests for normalcy (with corrective actions, such as data transformation, as necessary). We will also examine for patterns of missing data and dropout.

Baseline demographic and clinical characteristics will be compared for the buprenorphine (BPN) and placebo groups, using tests for differences in proportions (e.g., chi squared) and t-tests for continuous measures. If normality assumptions for continuous variables are not met even after appropriate data transformations, Wilcoxon rank sum tests will be used. These analyses will be employed to describe the study sample and also, to determine whether the randomization effectively balanced the two treatment groups with regard to baseline characteristics. If imbalances are found, it may be necessary to adjust for significant baseline differences when testing study hypotheses. Simple log-rank tests and Cox proportional hazard models will be the primary analytic approaches to compare time to remission among groups. If the number of remissions is small, then exact tests of proportions will be performed. Analyses will be conducted using the intent to treat (ITT) principle. We will examine dropout attributable to adverse events, utilizing data from Phase 2, with survival analysis (with censoring at time of dropout or removal from the study). This will include dropout due to patient decision as well as due to clinical decision. Mixed-effect models will be used to examine repeated Montgomery-Asberg Depression Rating Scale (MADRS) scores. Although a treatment development study is by definition not a formal test of efficacy hypotheses, it is consistent with the R34 mechanism for a pilot RCT to examine outcome data using appropriate statistical methods. Therefore, for dichotomous outcomes, treatment differences will be evaluated using logistic regression allowing for both unadjusted and adjusted analyses. Methods using generalized estimating equations (GEE) will be employed to test repeatedly measured discrete outcomes. For continuous outcomes, mixed effects models with site as a fixed effect will be performed to test for trajectory over time.

Our planned primary dichotomous outcomes are (1) remission rate (2) rate of serious adverse events, while our planned continuous outcomes are (1) Montgomery-Asberg Depression Rating Scale (MADRS) scores (2) side effect rating changes. We hypothesize that: 1) buprenorphine (BPN) will improve depressive symptoms, as compared to those assigned placebo, 2) buprenorphine (BPN) will be associated with low rates of side effects.

For the MRI data, we will use descriptive and inferential statistics. Comparison of data sets will include standard statistical analysis using a within subjects factorial ANOVA, T-test or multiple regression. All data points will be included.

3.1 Pharmacokinetics and Genetics involved in LL-TRD

Drug Level Monitoring: Pharmacokinetic changes associated with aging result in higher and more variable drug concentrations. Variability in treatment outcomes (efficacy or tolerability/safety) due to any cause (clinical or genetic) is more interpretable when also accounting for variable drug exposure. Thus, plasma levels will be collected for both venlafaxine and buprenorphine (BPN) at specific time points. Buprenorphine levels will be tested at beginning and end of Phase 2 for those randomized.

We will be collaborating with Evan Kharasch, M.D., a pharmacologist with expertise in buprenorphine pharmacokinetics. His lab will carry out buprenorphine blood level analysis.

4. Interventions and Risks:

4.1 Venlafaxine side effects

Infrequent to common: sustained hypertension, dizziness, vasodilatation, nausea, anorexia, weight loss, constipation, diarrhea, sexual dysfunction, excessive sweating, somnolence, insomnia, nervousness, tremor, dry mouth, and asthenia. In premarketing depression studies, 3% of subjects receiving venlafaxine XR, up to doses of 375 mg/d, developed sustained increase in blood pressure (defined as treatment emergent supine diastolic blood pressure >90 mg Hg and >10 mm Hg above baseline for three consecutive on-therapy visits). In premarketing depression studies, the mean increase of supine diastolic pressure in subjects receiving venlafaxine XR 75 mg/d to 225 mg/d was 1.2 mm Hg.
Rare: increased heart rate and hyponatremia.

4.2 Buprenorphine (BPN) side effects (experienced in a 16 week study at dose ~ 2 mg/day)
Common: (> 10%): asthenia, headache, diarrhea, insomnia, rhinitis, sweating.
Infrequent: (4-9%): chills, constipation, nausea, nervousness, runny eyes.
Rare: (</= 3%): dyspepsia, dizziness, and somnolence.

These buprenorphine (BPN) side effects are taken from the package insert and are from participants receiving buprenorphine (BPN) who were younger and receiving treatment for opioid dependence. This population is very different from our proposed sample of older adults who are not taking opioids. In general, we have observed that low-dose buprenorphine (BPN) is well-tolerated. The most common side effects we have observed are constipation, bloating, sedation, falls, confusion, G.I. upset, and in one instance, possible minor exacerbation of already present lower extremity edema.

Chronic exposure to opioids may negatively affect testosterone levels in men. The effect on sex hormones in women is inconclusive. Given the low dose (up to 1.2 mg/d) and relatively short duration of exposure to buprenorphine (BPN) (up to 16 weeks) in this project, we do not plan to monitor endocrine status. In future studies of buprenorphine (BPN) of longer duration, we plan to assess whether exposure of low dose buprenorphine (BPN) leads to alterations in endocrine status (e.g., testosterone and prolactin).

4.3 Risks of MRI:
Likely risks: There are no known physical risks to participants undergoing MRI scans who meet study inclusion and exclusion criteria. However, during scan and behavioral task procedures, patients may experience boredom or get tired.

Less likely risks: Because patients are asked to lie still during the scan they may experience mild muscle aches and pains. Participants are offered cushions to place at pressure points or beneath the knees to reduce discomfort. Participants will be exposed to the MRI scanner acoustic noise. They will be provided with earplugs to dampen the noise. Participants may feel anxious or even experience claustrophobia (fear of being in closed spaces) while in the scan. Participants are able to communicate with staff throughout the scan and are encouraged to tell the staff if they feel anxious and whether they want to interrupt or stop the scan.

Rare risks: Because the scanner uses a high strength magnet, subjects with ferro-magnetic metallic objects inside their bodies are at substantial risk. Metallic objects can be pulled by the magnetic field and cause physical harm. The following medical devices and body implants can be affected by the MRI field or be potentially hazardous in the MRI environment: cardiac pacemaker, implanted cardioverted defibrillator (ICD), aneurysm clip, implanted insulin/drug pump, neurostimulator (TENS unit), biostimulator/bone growth stimulator, hearing aid/cochlear implant, Gianturco coil (embolus coil), vascular clip, surgical clip or staples, heart valve prosthesis, Greenfield Vena Cava filter, middle ear implant, penile prosthesis, shrapnel or bullets, wire sutures, tattooed eye liner, body piercing jewelry, permanent contraceptive implants such as diaphragm/ UID and pessaries, intraventricular shunts, wire mesh, artificial limb or joint, any orthopedic item that is ferro-conductive

(ei, pins, rods, screws, nails, clips, plates, wire etc) dentures, any type of dental item held in place by a magnet, dental braces or any type of removable dental item, any other implanted item not mentioned. There may be unknown risks to the unborn fetus during pregnancy. Prior to the MRI, each subject will be carefully screened for the presence of any of these devices or implants.

4.4 Risk of precipitating substance abuse:

What is known and how will this be minimized? Buprenorphine is controlled as a Schedule III narcotic under the Controlled Substances Act. Buprenorphine is a partial agonist at the mu-opioid receptor. Chronic use may produce dependence as well as withdrawal symptoms. In our pilot work, we have seen no evidence of abuse/dependence or withdrawal effects.

During our pilot work, patients have not described euphoria, drug craving, or physical or psychological difficulty with stopping the medication after completing the study. A benefit of studying older adults is that most opioid-abuse disorders have been declared by old age, and we will exclude subjects with a history of opioid dependence, serially assess subjects for euphoria, closely monitor all prescribed study medication, and require that unused tablets be returned to the pharmacy for destruction (to minimize the risk of diversion). However, there is still a risk of precipitating a de novo abuse/dependence diathesis. We have observed that 22.4% of patients with LL-TRD have a history of alcohol mis-use. These subjects may be at increased risk of opioid mis-use. For all subjects, we will closely monitor for the emergence of change in alcohol use. We will use the Alcohol Use Disorders Identification Test (AUDIT) as deemed clinically necessary to assure there is not a clinically significant change in alcohol use. The euphoria measure will be administered at a number of time points. If subjects endorse euphoria, the dose of study medication will be decreased. At the end of the study, the study medication will be tapered approximately 20% every 3 days until it is discontinued. Subjects will be monitored by telephone for the week following discontinuation using the Clinical Opiate Withdrawal Scale (COWS) to assess for symptoms of withdrawal. They will also be encouraged to contact the research staff/ P.I. if they experience symptoms of withdrawal (about which they will be counseled). If symptoms emerge, we will then restart the study medication at the last dose and begin another slowed taper. All subjects will be monitored for at least one week after discontinuation of the study medication to assure they are comfortably off the medicine. Aftercare resources will be determined on a case-by-case basis with the subject. All subjects will be counseled during the informed consent process about the low but possible risk of becoming dependent upon the study medication during their participation. Our DSMB will help us monitor the emergence of such problems.

One of our primary aims is to evaluate the acceptability of the augmentation of venlafaxine XR with buprenorphine (BPN), and we will closely monitor all subjects for any serious adverse events (SAE). Thus, we believe that subjects treated under the controlled conditions of the proposed protocol will actually be safer than subjects receiving many augmentation strategies in the community under usual care conditions. The potential risks associated with participation (including the risk of the augmentation and the risk of receiving an ineffective treatment) will be clearly described to all the potential subjects as part of the informed consent process.

4.5 Suicide:

Patients who are identified as being acutely suicidal will be excluded from the study. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all subjects eligible to participate in this study are statistically at a relatively higher risk for suicide than the general population. However, the subjects' absolute risk for completing suicide during this brief study remains very low (i.e., about 1 in 3,000 to 10,000) and participation in the study does not create or increase the risk of completed suicide. Actually, most experts believe that one of the most efficient ways to decrease suicidal risk in older depressed individuals is to treat their depression. Even though we predict that the depression of subjects randomized to buprenorphine (BPN) is more likely to resolve than the depression of those randomized to placebo, this hypothesis still needs to be confirmed, which is beyond the scope of this developmental trial.

As discussed in the Assessments section, at each assessment point, the trained raters will probe for passive death wish, and suicidal ideation, intent or plan when they administer the Montgomery-Asberg Depression Rating Scale (MADRS) and the Scale for Suicidal Ideation (SSI). If a subject endorses suicidal ideation, intent, or plan, the rater will be trained to follow an operationalized protocol that has been developed to manage high-risk subjects in other studies of depressed subjects potentially at risk for suicide. This protocol has already been used successfully by investigators to manage several acutely suicidal patients and it has been published.[35] Briefly, the protocol entails a specific determination of the suicidal risk and prescribes a set of actions. For instance, when a subject is determined to be at high and immediate risks, the rater is instructed to stay with the subject until he or she has contacted a study psychiatrist to discuss the situation and to devise a plan. For this reason, raters will have cell phones and at least one study psychiatrist will be reachable at all times. In case of extreme emergency, raters are instructed to call their hospital security team or 911 for immediate help and to initiate commitment proceedings.

The ethical ground for the use of a "placebo" condition in studies involving depressed subjects who are at risk for suicide has been reviewed.[36] Furthermore, all participants will be formally assessed weekly during the study. We have a 24/7/365 on-call system with geriatric psychiatry back-up. If the study personnel identify that a subject has become acutely suicidal, this subject will be referred to a mental health professional for further evaluation and treatment. This may lead to a clinical intervention that is lifesaving and may not have occurred had the subject not been participating in the study. Continued use of venlafaxine during phase 2 of the study may also provide protection from suicide, as antidepressants have been shown to decrease the risk of suicide in older adults.[37]

4.6 Procedures to Minimize Risk: The PI will have primary responsibility for the monitoring of subjects during the entire time they participate in the study. Subjects will be reviewed at baseline by the PI; exclusion criteria will reduce the risk to subjects. The study will have a 24-hour answering service with physician backup. The study investigators, study coordinators, and other study staff will meet weekly to review accrued data, data confidentiality, adherence to protocol design, recruitment, and subject complaints. During this meeting, all subjects will be clinically reviewed, including discussion of clinical presentation, changes in clinical symptoms, side effects, any possible adverse events, and intercurrent medical conditions. During these discussions, any possible changes to the risk-benefit level will be discussed.

The first dose of study medication (buprenorphine (BPN) or placebo) will be taken at home. Participants will be encouraged to not use alcohol during participation in the project, minimize driving or the operation of heavy machinery for the day of and immediately following dose escalations, and to keep the study medication in a secure and/or locked place.

4.7 Procedures to Minimize Risk of MRI:

To minimize the risk of boredom, tiredness, muscle aches and anxiety, participants may take breaks as needed throughout the study. They will also be told they can take breaks. Participants are offered pillows and blankets to alleviate discomfort in the scanner. Participants will be able to communicate with study staff at all times during the scan and will be told they can stop the scan at any time for any reason. Earplugs will be offered to decrease the exposure to the scanner's acoustic noise.

Participants will be screened at the time of the phone screener and again before the MRI scan for any contraindications to the MRI, including the presence of implanted devices that pose a substantial risk. The scanning bay on the CCIR is located inside the hospital thus facilitating access to the hospital emergency personnel should a medical emergency arise.

4.8 Discomfort With Answering Questionnaires: With respect to minimizing the discomfort that may result from the interview, raters have been or will be selected on the basis of personal attributes and interpersonal

skills as well as substantive knowledge. They will be further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects. Furthermore, they are trained to recognize signs of significant stress or irritability and will be instructed that they should gently terminate the interview whenever distress is observed.

4.9 Side Effects and Adverse Events: Regular assessments for side effects including sedation, falls, constipation, and mental slowing will be routinely conducted. If present, they will be assessed by a physician. Regular feedback will be provided to the subjects and their treating physicians. At any time during the study if a subject is judged to be experiencing serious side effects by the treating or research physician, he or she will be withdrawn from the study and the appropriate referral will be recommended.

4.10 Data Integrity and Confidentiality: Subjects will be interviewed specifically to obtain research data. In addition to training and close supervision of research staff described above, a formal quality control mechanism will provide a systematic check on the quality of interview data. Specific procedures to protect subjects' confidentiality, and formal mechanisms limiting access to information that can link data to individual subjects include: Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research coordinator at the time consent is signed, will represent subjects during data entry, data transfer, data analysis, or other file management procedures. To facilitate tracking, a password-protected computer file will be maintained containing the identity of subjects, their ID numbers, and information about how they can be reached. This file, however, will contain no clinical data. Only members of the investigative group will have access to secured files or to master lists for subject code numbers and will be well-informed regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project.

Clinical information obtained at initial evaluation, and clinical treatment notes, will become part of subjects' medical records. Modern medical record facilities are maintained that provide adequate safeguards for the protection of confidentiality of medical records.

Research team members will enter study data via a secure Web site into a SQL/Server relational database. At point-of-entry, data values will undergo consistency edits (e.g., ID validation, range verification, duplicate detection) and personnel will be required to correct errors. RedCap will be used to create reports, also via the Web-based program.

4.11 Risks in Relation to the Anticipated Benefits

All subjects participating in this study will receive a comprehensive assessment performed at the time of initiation of the study. In addition, subjects will be assessed at regular intervals. As discussed above, these research assessments may reveal conditions that had not been identified (e.g., suicidality, psychosis, or mania), leading to critical clinical intervention that would not have occurred otherwise. All subjects will be treated openly with venlafaxine and some will be randomized to buprenorphine (BPN) or placebo. They may benefit from these interventions if indeed they are effective. Regardless of whether the main hypotheses are supported, the results of this study should be useful in determining the safety and clinical effect of venlafaxine plus buprenorphine (BPN) for the treatment of LL-TRD. These results will guide the use of this combination in clinical settings. If it is shown to be dangerous or ineffective, knowledge derived from this project could help to reduce its use. Conversely, if it is shown to be safe and effective, this knowledge will support the treatment of older patients with LL-TRD and thus, contribute to reduce the significant public health burden associated with LL-TRD. Moreover, subsequent studies can then compare the relative effectiveness, tolerability, and acceptability of this intervention and other pharmacotherapies or psychotherapies. Finally, comparative studies can lead to additional research investigating the use of venlafaxine plus buprenorphine (BPN) in other "complicated" forms of late-life depression (e.g., bipolar depression, psychotic depression). As the overall risks involved in participating in this study are deemed relatively small because of the protections described above, the risk to benefit ratio for this project is perceived to be low and justifies its implementation.

Adverse events, assessment of changes to the risk/benefit ratio, acceptability of study continuation, breaches in confidentiality, and subject complaints will be reviewed by the principal investigator and reported to the IRB in accordance with guidelines. Any change in risk-to-benefit ratio will be provided to currently active subjects, and once a modified consent form is approved by the IRB, active subjects will be re-consented if they decide to continue, and any new subjects will be consented with the new consent form.

Data and Safety Monitoring Plan
A summary of the data and safety monitoring frequency and outcome will be submitted yearly to the IRB at time of obtaining renewal approval. Adverse events, assessment of changes to the risk/benefit ratio, acceptability of study continuation, breaches in confidentiality, and subject complaints will be reviewed by the principal investigator and reported to the IRB in accordance with IRB reporting guidelines. Any change in risk-to-benefit ratio will be provided to currently active subjects and once a modified consent form is approved by the IRB, active subjects will be re-consented if they decide to continue, and any new subjects will be consented with the new consent form.

Briefly, major depression is a serious disorder that can lead to suicide and other significant adverse consequences. We also recognize that our interventions could expose some subjects to risks that have not been identified thus far. Therefore, the presence of an independent DSMB is critical. The DSMB will include experts in late-life depression, substance abuse/ dependence, and a biostatistician. The functions of the DSMB have been designed to ensure the safe and effective conduct of research projects and to recommend conclusion of a trial when significant benefits or risks are identified, or if it becomes unlikely that the trial can be concluded successfully. The DSMB will assure that the investigators submit reports of all unexpected adverse events and of all serious adverse events to the IRB and to the DSMB itself. The DSMB will in turn inform the IRB of its relevant deliberations and the final determination. The DSMB will also decide when adverse events require reporting to the NIH. If applicable, the DSMB will also send to the IRB copies of all communications with the NIH.

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