Incomplete Response in Late-Life Depression: Getting to Remission With Buprenorphine

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Study Protocol

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Study Protocol: 100 subjects, of both sexes and all races, will be asked to participate in this project.

This study has 2 phases. The core of this project is in the second phase: a randomized, placebo controlled, double blind parallel group comparison of venlafaxine XR plus buprenorphine with venlafaxine XR plus placebo for Treatment Resistant Late Life Depression (TRLLD).

Phase 1: We will prospectively determine treatment resistance by initially treating participants with a 12-week course (up to 16 weeks) of open-label venlafaxine XR. This is the same lead-in treatment as in our completed IRL-GREY multi-site R01 for TRLLD, and we have found it to be highly successful. We will have up to 100 participants 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 with venlafaxine will exit the study; non-remitters will be eligible for the RCT of BPN vs. placebo augmentation. Visits and assessments during open-label lead-in are weekly for the first two weeks and then every 2 weeks. Assessments may be completed by phone if necessary. If assessment is done by phone, vitals will not be collected at that timepoint.

In patients who are already on venlafaxine when they start the protocol, the titration can be faster with an increase to 300 mg/day after only 4 weeks. To assess remission status, we want to be able to follow subjects for at least 4 weeks on 300 mg/day or the maximum tolerated dose (because less than that will have been an inadequate exposure to rigorous first line antidepressant pharmacotherapy. Subjects who enter the study on venlafaxine and are already on their highest tolerated dose need to be maintained on this dose for at least 4 weeks before they are eligible for RCT (phase 2).

Phase 1 can be extended up to 16 weeks to assure we have prospectively documented treatment non-response. Patients must have at least 4 weeks at the highest tolerated dose in order to have been declared a non-responder (because less than that will have been an inadequate exposure to rigorous first line antidepressant pharmacotherapy). They need to have 2 weeks of MADRS less than or equal to 10 in order to be declared a responder (thus the flexibility to extend phase 1 to 16 weeks to assure true treatment resistance).

Phase 2, RCT Overview: In the 8-weeks of BPN vs. placebo, thirty 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 BPN or placebo. The reasons for using a 2:1 random allocation include: 1) collection of more data about plasma levels of BPN and its metabolites, 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 timepoint is that clinicians may become unblinded because they are also assessing side effects.

At the beginning of phase 2, participants will be asked to review and sign the phase 2 contract (attached under other attachments in OSIRIS). This contract outlines safety precautions and directions for taking and storing the medication. This contract will be signed with all participants who are moving into phase 2.

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 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 8-week period (defined by a MADRS score of 10 or lower for two consecutive weeks, as in the IRL GREY study). The first dose of buprenorphine will be taken while in the office while under the supervision of the PI, Co-I, and study personnel. They will wait in the office for 60 minutes after taking the initial buprenophine dose.

Since the analgesic effects of BPN may obscure the antidepressant effects, we will exclude subjects with severe pain. This will be defined as a score of greater than 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).

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. Blinded independent assessors will be used to confirm treatment response. The rationale for this is described above.

Titration schedule of BPN: Dosing increases will be guided by antidepressant response (e.g., 2 consecutive MADRS scores less than 10) and our protocolized use of the Frequency, Intensity, and Burden of Side Effect Rating (FIBSER) Scale score. This individualized dosing regimen accommodates both antidepressant response and tolerability. We have used it successfully in our BPN pilot work, an ongoing study of the pharmacotherapy of complicated grief, and it was used in the STAR*D project (Steffens et al, 2010). We will increase the dose by 0.2 mg/week up to 1.2 mg/day based on MADRS and FIBSER scores. Our rationale for selecting this dosing schedule is based on other small open-label trials using BPN for treatment resistant depression

in younger patients in which the initial dose ranged from 0.15 mg/day (intranasal formulation) – 0.4 mg/day (sublingual), and was increased to 1.8 mg/day (intranasal) – 2 mg/day (sublingual). The duration of previous studies has ranged from 1 week to 4 weeks, with the dose increased by 0.4 mg/day every 1-2 days or according to tolerance and clinical benefit. In our recently completed work, the duration of exposure to BPN has been 8 weeks with a maximum dose of 1.6 mg/day.

Consistent with the developmental aim to learn more about dosing ranges and plasma levels, we will extend phase 2 to eight weeks with a maximum dose of 1.2 mg/d.). With this approach, we expect to clarify the range of efficacious and tolerable doses for 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 phase 3. 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 BPN. This may be due to the relatively short duration of exposure and the very low doses used in the project.

Breaking the blind: The blind will be broken for all participants at the end of phase 2.