



## **Reducing Suicidal Ideation through Treatment of Nightmares-PTSD (REST-ON-PTSD)**

### **Clinical Protocol**

**Version 1.2  
April 6, 2015**

**Principal Investigator:  
W. VAUGHN MCCALL, M.D., MS**

## Project Summary

Numerous (>40) epidemiologic reports have linked insomnia and nightmares to suicidal ideation and suicide death. We are presently engaged in a project which tests the hypothesis that treatment of insomnia in depressed patients with hypnotic medications will reduce the intensity of suicidal ideation. This ongoing project is called Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT).

We have now acquired and analyzed new data since the inception of the present project that reveals that nightmares and disturbing dreams are more strongly related to the intensity of suicidal ideation than is insomnia itself. We therefore propose to target treatment of nightmares in suicidal patients experiencing nightmares as part of post-traumatic stress disorder (PTSD). This new effort is named Reducing Suicidal Ideation Through Treatment of Nightmares in PTSD (REST-ON-PTSD). REST-ON-PTSD will offer treatment with open label selective serotonin reuptake inhibitors (SSRIs) for PTSD, or open label treatment for bipolar disorder, combined with randomization to prazosin versus placebo. SSRIs are the only medications approved by the FDA for treatment of PTSD, while prazosin is the best-practice pharmacologic treatment for nightmares.{Aurora, 2010 1365 /id} REST-ON-PTSD is designed to be a small, randomized controlled clinical trial intended to generate pilot data to estimate effect sizes for prazosin treatment in reducing suicidal ideation in suicidal PTSD outpatients who have nightmares and disturbing dreams, with the following Specific Aims:

Primary Aim: We will estimate the effect size of prazosin on the intensity of suicidal ideation in PTSD outpatients with nightmares and disturbing dreams.

Hypothesis 1. Prazosin, combined with an SSRI or open label treatment for bipolar disorder, will reduce suicidal ideation in suicidal PTSD outpatients who have nightmares and disturbing dreams.

Secondary Aim: We will estimate the effect size of prazosin in reducing the intensity of nightmares and disturbing dreams in suicidal PTSD outpatients with nightmares and disturbing dreams.

Hypothesis 2. Prazosin, combined with a SSRI or open label treatment for bipolar disorder, will reduce the intensity of nightmares and disturbing dreams in suicidal PTSD outpatients with nightmares and disturbing dreams

Tertiary Aims: We will assess the safety of prazosin in the treatment of suicidal PTSD outpatients with nightmares and disturbing dreams. We will assess the impact of prazosin in salivary amylase, which is a test of systemic adrenergic tone.

Impact on the Field This application has the potential to change providers' practice in the approach to treating PTSD patients with mild-moderate suicidal ideation. Physicians have limited options in pharmacologic approaches to reduce suicide risk. The success of prazosin in reducing suicidal ideation in PTSD patients would be a novel strategy for a serious public health problem with few known solutions.

### 3. RESEARCH STRATEGY

#### 3.a. Significance

Suicide is a leading cause of death across all ages and occurs at a rate of 10-11 cases per 100,000 persons per year in the USA.{Mann, 2005 819 /id} It is the third-leading cause of death in the USA in those under 30 years of age.{Mann, 2005 819 /id} Across the world, the rank order of suicide in global mortality has risen between 1990 to 2010 from the 14<sup>th</sup> to 13<sup>th</sup> place in cause of death. An estimated 883,000 persons died by suicide around the world in 2010. {Lozano, 2012 1364 /id} Most suicides occur in the context of an active psychiatric disorder.{Mann, 2005 819 /id}

Suicide rates in the US military have drawn recent scrutiny as it has been revealed that more American service men died of suicide in 2012 than died of battle wounds in Afghanistan. Recent expert reports indicate that suicide death is indeed higher in US war-veterans as compared with non-military age-matched controls, that young men have the highest age-adjusted disproportionate risk, and that Iraq deployment indicates an especially high risk.{Krysinska, 2010 1373 /id;Rozanov, 2012 1376 /id} The standard mortality ratio (SMR) for the entire US Army was actually lower than expected until 2008, at which time the SMR exceeded 100, and in 2009 the SMR was estimated at 115.3 (95% CI 113.5-117.1).{Behavioral and Social Health Outcomes Program, 2012 1378 /id}

At least some of this elevated risk among returning war veterans is believed to be explained by post-traumatic stress disorder (PTSD), a mental disorder distinguished by reliving traumatic experiences, heightened physiologic arousal, and emotional numbing. Again, there is some debate as to whether PTSD is linked to excess suicide death, but there is a consensus that it is linked to elevated suicidal ideation and suicide attempts, and {Krysinska, 2010 1373 /id;Rozanov, 2012 1376 /id} during Vietnam PTSD represented a 4-fold increased risk for suicide.{Rozanov, 2012 1376 /id} Although >50% of persons with PTSD also meet criteria for MDD,{Post, 2011 1372 /id} and while the risk of suicide is further amplified by the presence of major depressive disorder (MDD), PTSD is still an independent risk factor for suicide.{Krysinska, 2010 1373 /id;Rozanov, 2012 1376 /id}

Risk factors for suicide include both unmodifiable and some potentially modifiable factors.{Maris, 2002 1011 /id;Coryell, 2005 674 /id;Brown, 2000 314 /id} Examples of unmodifiable factors are advancing age, male gender, and Caucasian ethnicity. Potentially modifiable risk factors include symptoms of depression, hopelessness, social isolation, active alcohol/substance use, and severe sleep disturbance. As a predictor, insomnia is stronger than a specific suicide plan in predicting near-lethal suicide attempts,{Hall, 1999 801 /id} yet sleep disorder is often overlooked in reviews of risk factors for suicide and suicide prevention.{Oquendo, 1997 1019 /id} The need to broaden the search for modifiable risk factors is epitomized by this recent statement: "nowhere is the lack of proven therapeutic methods greater than in the prevention of suicidal behavior."{Oquendo, 2003 1018 /id}

As we have reviewed elsewhere,{McCall W Vaughn, 2011 1253 /id;McCall, 2010 1193 /id;McCall WV, 2013 1475 /id} >60 research studies link insomnia to suicidal ideation, suicidal behavior, or suicide death, including >40 studies in adults. {Barraclough, 1975 926 /id;Agargun, 1997 805 /id;Agargun, 1997 8 /id;Agargun, 1998 804 /id;Smith, 2004 799 /id;Bernert, 2005 798 /id;Chellappa, 2007 892 /id;Bernert, 2009 1044 /id;Agargun, 2007 891 /id;Sjostrom, 2007 752 /id;Goodwin, 2008 1013 /id;Fawcett, 1990 76 /id;Tanskanen, 2001 797 /id;Fujino, 2005 809 /id;Turvey, 2002 397 /id;Li, 2010 1196 /id;Tishler, 1981 929 /id;Bailly, 2004 933 /id;Choquet, 1989 808 /id;Choquet, 1993 807 /id;Liu, 2004 928 /id;Vignau, 1997 806 /id;Roberts, 2001 803 /id;Cukrowicz, 2006 927 /id;Barbe, 2005 931 /id;Goldstein, 2008 930 /id;Nadorff, 2011 1197 /id;Bjerkeset, 2011 1246 /id;Brower, 2011 1247 /id;Krakow, 2011 1248 /id;Carli, 2011 1249 /id;Fitzgerald, 2011 1254 /id;Agargun, 2003 828 /id;McCall, 2010 1193 /id} Insomnia and nightmares were the most common sleep disturbances associated with suicide, even after adjusting for severity of depression. Five studies were prospective and showed that insomnia was a risk for suicide death. {Fawcett, 1990 76 /id;Tanskanen, 2001 797 /id;Fujino, 2005 809

/id; Turvey, 2002 397 /id; Bjerkeset, 2011 1246 /id} The clinical association of insomnia, nightmares, and suicidal ideation is paralleled by the physiologic finding that, among depressed outpatients, there is an inverse relationship between REM sleep latency and intensity of suicidal ideation.{Agargun, 2003 828 /id} A higher rate of depressed patients report unpleasant dreams (39%) as compared with persons who are not depressed (14%), even when both the depressed and nondepressed persons share similar life circumstances.{Cartwright, 1996 1371 /id} Whether the depressing dreams of depressed patients are conceptually the same as the nightmares of PTSD is unclear, although it is clear that bad dreams are a risk factor for suicidal ideation, independent of a PTSD diagnosis.{Nadorff, 2011 1197 /id}

Selective serotonin reuptake inhibitors (SSRIs) are a mainstay treatment for PTSD, and two of these, sertraline and paroxetine, are FDA approved for PTSD. However, SSRIs do not address all PTSD-symptoms equally well. For example, SSRIs are beneficial for symptoms like irritability, and but do less for sleep disturbance.{Baker, 2009 1375 /id} Abnormal, elevated activity within the brain's noradrenergic system is believed to play a role in the symptoms of hyper-arousal, such as nightmares, and SSRIs do not directly impact the noradrenergic system.{Krystal, 2009 1374 /id} In contrast, FDA-approved, foundational treatments for bipolar disorder include lithium, valproic acid, lamotrigine, quetiapine, asenapine, olanzapine, ziprasidone, lurasidone ,and the olanzapine-fluoxetine combination.<sup>54</sup>

Given these facts, we propose that dampening the hyperarousal of PTSD with a blocker of noradrenergic receptors, would lead to less problematic nightmares, and culminate in lesser intensity of suicidality thinking.

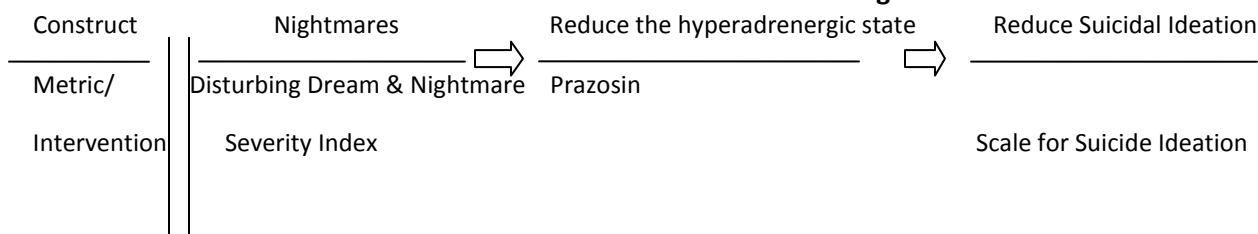
The American Academy of Sleep Medicine states that the best-practice pharmacologic treatment for nightmares is prazosin.{Aurora, 2010 1365 /id} Prazosin is an  $\alpha_1$  adrenergic receptor blocker approved for use as an antihypertensive. The cardiovascular effects of the drug were fully characterized more than 30 years ago.{Colucci, 1982 1369 /id} The drug is slowly titrated starting with 1-mg capsules in order to minimize the risk of hypotension, with an average dose of 6-15 mg per day for antihypertensive effects. It generally has no effect on heart rate. The most common side effects at these doses are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%.

A number of randomized controlled comparisons of prazosin have proven that prazosin is superior to placebo in reducing nightmares. These studies have been primarily in the study of PTSD-related nightmares, with some preliminary information suggesting that prazosin may also reduce non-nightmare awakenings in PTSD patients.{Thompson, 2008 1367 /id} The most recent large study of prazosin for PTSD-related nightmares in American soldiers found that a mean bedtime dose of  $15.6 \pm 6.0$  mg in men, and  $7.0 \pm 3.5$  mg in women, reached over a period of 5-6 weeks, was highly effective, with blood pressure changes, as compared with placebo. The most common side effects in this study were lightheadedness (25% versus 20% for placebo) and nasal congestion (22% versus 11% for placebo).{Raskind, 2013 1474 /id}

### 3.b. The theoretical model

One of the favored models for the etiology of insomnia posits that hyperarousal leads to sleep loss. In other words, it is not the sleep machinery that is broken in insomnia, but rather an awake system that is in overdrive and is inhibiting the expression of sleep, via an overactive sympathetic nervous system.{Bonnet, 2010 1366 /id} The hyperarousal model of primary insomnia resonates with hypervigilence and hyperstartle reactions as core symptoms of PTSD, and is congruent with the finding that these sympathetic-autonomic symptoms are relieved by prazosin, an  $\alpha_1$  adrenergic receptor blocker. Sympathetic-autonomic hyperarousal may be a common pathway for insomnia, nightmares, and suicide risk. Therefore, our theoretical model (Figure 1, below) is that treatment of nightmares and disturbing dreams with an  $\alpha_1$  adrenergic receptor blocker leads to reduced intensity of suicidal ideation.

Figure 1

**Theoretical Model of Mediation of the Effect of Nightmares on Suicidal Ideation**

The expert workshop on suicide prevention concluded that “randomized controlled trials of psychopharmacology are needed in suicide prevention studies.”{Mann, 2005 819 /id} Targeted treatment of nightmares may represent one such avenue. We show in our Preliminary Studies that (1) the relationship between sleep disturbance and suicidal ideation holds true within the context of depression clinical trials, (2) nightmares and disturbing dreams about sleep mediate risk for suicidal ideation in insomniacs.

**3.c. Innovation**

We reported the first clinical trial examining insomnia and suicide risk.{McCall, 2010 1193 /id} While all pharmacologic interventions targeting suicide risk are innovative and important, targeting nightmares as a modifiable risk factor for suicidal ideation is especially innovative. Despite dozens of reports of association between sleep insomnia and suicide, there are no completed psychopharmacology trials targeting nightmares for suicide risk reduction. Our ongoing study, REST-IT, is the first multi-site intervention for insomnia as a means to reduce suicidal ideation in depressed, suicidal, insomniacs. The present proposal, REST-ON-PTSD, will target treatment for nightmares and disturbing dreams as a second avenue for reducing suicidal ideation. We will test the impact of prazosin on suicidal thinking, and as part of our innovation, we will test whether improvement is mediated via reduction in nightmares and disturbing dreams.

**3.d. How this project will improve knowledge and practice**

This project is consistent with the August 2010 Report of the National Advisory Mental Health Council’s Workgroup, “From Discovery to Cure”, which emphasized the importance of advancing ‘personalized treatment’ and ‘preemptive treatment’ (page 3).{Leon, 1999 1256 /id} The emphasis of this Report is evident in our proposal as we identify nightmares as a symptom of particular relevance in some, but not all suicidal patients, and deserving of targeted intervention, leading to a preemptive reduction in nightmares and disturbing dreams, and presumably, suicidal ideation. In Recommendation 2.4.1, the Report also calls for support for clinical trials which show that (a) “the adaptation [i.e., intervention] changes a factor [nightmares] that has been associated with ....partial response [suicidal ideation], and (b) clear explication of the mechanism by which the moderator variable [nightmares] functions to disadvantage... a subgroup [suicidal PTSD outpatients with nightmares]. This project meets the needs expressed in the Report.

**3.e. Approach****3.e.1 Preliminary Studies****Relationship between insomnia and suicidal ideation during a 10-week clinical trial**

We consented 60 depressed insomniacs to participate in a study examining the value of adding a hypnotic medication to a SSRI.{McCall, 2010 1149 /id} After a week of baseline assessment, patients received one week of open-label fluoxetine (FLX) monotherapy, starting at 20 mg in the morning. Patients still reported insomnia after one week of FLX and continued on with 8 more weeks of open label FLX, and were also randomized to also receive either the hypnotic eszopiclone (ESZ) 3 mg or placebo given on a double-blind

basis at bedtime. Patients who still had a 24-item Hamilton Rating Scale for Depression (HRSD24) {Hamilton, 1960 371 /id}  $>15$  at the end of 4 weeks of randomized treatment could choose to take 40 mg FLX for the next 4 weeks. Study endpoints included measures of sleep, mood, and suicidal ideation. Insomnia severity was graded by the Insomnia Severity Index (ISI). {Bastien, 2001 639 /id} Suicidal ideation was measured with the Scale for Suicide Ideation (SSI). {Beck, 1979 18 /id; Beck, 1997 19 /id; Beck, 1999 20 /id}

Participants were 18-70 years old, with either (a) sleep latency  $> 30$  minutes and sleep efficiency  $< 85\%$  at least 4 nights per week. {Edinger, 2004 553 /id} All participants met a DSM-IV diagnosis of unipolar MDE per Structured Clinical Interview for DSM-IV (SCID), {American Psychiatric Association, 1994 286 /id} and a HRSD24 score  $\geq 20$ . {Hamilton, 1960 371 /id} All participants completed one night of baseline polysomnogram (PSG) which showed no clinically significant sleep apnea (Apnea/Hypopneas index  $>15$ ) or Periodic Limb Movement Disorder (PLM arousal index  $>15$ ), following standard measurement procedures described elsewhere. {McCall, 2009 1052 /id}

The average age of the randomized sample was  $41.5 \pm 12.5$  years, and 66% were women, with 23.2% minorities. At baseline, the average HRSD24 score was  $27.1 \pm 3.9$ , and the average ISI score was  $20.7 \pm 4.0$ . Scale for Suicide Ideation (SSI) scores were analyzed using generalized linear mixed models for repeated measures with predictor variables being insomnia (ISI scores), the mood item, and the anhedonia item from the HRSD24. Baseline SSI was  $3.7 \pm 5.2$ , with 55% having a SSI score  $\geq 1$ , and 37% of patients having a SSI score  $\geq 3$ .

The model with ISI as the predictor for SSI was significant with the regression coefficient corresponding to ISI being positive ( $\beta=0.055$ , SE=0.02,  $p<0.01$ ). Other univariate models found that the depressed mood item was also a significant predictor of suicidal ideation ( $p<0.005$ ), but anhedonia was not a predictor of suicidal ideation ( $p=0.9$ ). A multivariate model simultaneously including both the insomnia and the depressed mood items found that both were independent predictors of suicidal ideation (both  $p<0.05$ ). Our findings confirm that the intensity of insomnia predicts intensity of suicidal ideas during a clinical trial of MDE, even after adjusting for depressed mood and anhedonia. {McCall, 2010 1193 /id}

#### Suicidal ideation is mediated by nightmares

In a new study we have recently reported that the relationship between insomnia and suicide is mediated through nightmares and disturbing dreams. {McCall, 2013 1348 /id} We collected cross-sectional data on 50 adults (mean 55 y.o.) in various stages of active depression or recovery, including 16 psychiatric inpatients and 23 outpatients and 11 emergency psychiatry patients. Bad dreams were measured with the Disturbing Dreams and Nightmare Severity Scale (DDNSI), while the intensity of suicidal ideation was measured with Scale for Suicide Ideation (SSI). {Beck, 1979 18 /id; Beck, 1997 19 /id; Beck, 1999 20 /id} DDNSI was significantly related to SSI ( $r=0.60$ ,  $p<0.001$ ), and in a mediation analysis we found that the relationship between insomnia and suicidal ideation was in fact mediated in part by disturbing dreams and nightmares. These results support the premise that nightmares mediate insomnia as a risk factor for suicidal ideation in depressed patients. Using a receiver operating curve, we also found that emergency psychiatry patients are best discriminated from outpatients by a Scale for Suicide Ideation score of 16, and while the outpatients and emergency patients were best separated by a Disturbing Dreams and Nightmare Severity Scale score of 6 ( $p<0.001$ ).

### METHODS OF THE PRESENT PROPOSAL

#### 3.e.2. OVERVIEW

This pilot study will enroll 20 participants with PTSD who have prominent problem with nightmares and a mild-to-moderate degree of suicidality. Participants will have been on a stable dose of an SSRI or open label treatment for bipolar disorder, at a therapeutic dose, for at least one month before baseline assessment. Patients with bipolar disorder will have been on a stable dose of FDA-approved treatment for bipolar disorder

(lithium, valproic acid, lamotrigine, quetiapine, asenapine, olanzapine, ziprasidone, lurasidone or the olanzapine-fluoxetine combination). Patients who meet all qualifying requirements at baseline will then be randomized in a 1:1 proportion to either prazosin 1 mg at bedtime or placebo. Over the course of 6 weeks, the dose of prazosin will be increased as tolerated, while the dose of the SSRI or medication for bipolar disorder is held constant. Participants will be re-assessed weekly for 8 weeks post-randomization, and only enough prazosin will be provided to last until the next visit.

### **3.e.3. Participants**

**Inclusion criteria:** Participants are 18-65 years of age, including both men and women. The local project manager confirms a DSM-IV-TR diagnosis of PTSD by SCID and by the Clinician Administered PTSD Scale (CAPS).{Weathers, 2001 1377 /id} The participant must have a least a moderate degree of nightmare severity, as indicated by a Disturbing Dreams and Nightmares Scale score of  $\geq 10$ .{Krakow, 2002 1368 /id}

Participants must provide their own written, informed consent. Participants will have a mild-moderate level of suicidal ideation defined as a SSI score  $\geq 3$  but will not have imminent intent to commit suicide consistent with a Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation level of  $< 4$ .{Oquendo, 2003 1018 /id} All participants will have been on a stable dose of a SSRI for at least 4 weeks before baseline assessment, at a dose equivalent to fluoxetine 20 mg (i.e., sertraline 50 mg, paroxetine 20 mg, etc.), or if the patient has a diagnosis of bipolar disorder, they must be on a stable dose of an FDA-approved bipolar medication for at least 4 weeks (lithium  $> 300$ mg daily, valproic acid  $> 500$ mg daily, lamotrigine  $> 50$ mg daily, quetiapine  $> 100$ mg daily, asenapine  $> 10$ mg daily, olanzapine  $\geq 5$  mg, ziprasidone  $\geq 20$  mg, lurasidone  $\geq 40$  mg or the olanzapine-fluoxetine combination)Other psychotropics, including additional antidepressants, mood stabilizers, benzodiazepines, and antipsychotics are permitted as long as no dosage changes are anticipated during the randomized treatment with prazosin. A co-morbid diagnosis of major depression is permitted, as well as diagnoses of generalized anxiety, panic disorder, social phobia, and obsessive compulsive disorder.

Participants sexual orientation and gender will be assessed with the following form:

1. Do you consider yourself to be:

- Heterosexual/straight
- Gay/lesbian/homosexual
- Bisexual
- Not sure
- Decline to state

2. What is your gender? (check all that apply)

- Male
- Female
- Transgender, Male-to-Female (MTF)
- Transgender, Female-to-Male (FTM)
- Transgender, do not identify as male or female
- Not sure
- Decline to state

**Exclusion criteria:** Participants are excluded if they have an active diagnosis of alcohol or substance abuse within the last 90 days, active episode of bipolar mania or hypomania, or lifetime diagnosis of schizophrenia per the SCID. Patients with a clinical diagnosis of major neurocognitive disorder or a MMSE  $\leq 24$ , will be excluded.

Additional exclusion criteria

- History of sensitivity or allergy to prazosin or quinazolines

- History of fainting or syncopal episodes in the last 6 months
- History of hypotension
- Automatic Blood Pressure readings with systolic BP <90, or diastolic <50, either sitting or standing.
- Planned use of sildenafil, tadalafil, or similar erectile dysfunction medications

### 3.e.4. Treatment

#### Dose finding during randomized care

Participants who pass all screening and baseline-week assessments immediately begin one capsule of prazosin 1 mg capsule or a placebo. Study drug will be taken at bedtime. Participants will be called by study-staff after two nights, and if participants do not appreciate an improvement in their disturbing dreams and nightmares after 2 nights, then they are allowed to increase their bedtime study drug to two capsules, following the design of Raskind et al (Table 1).{Raskind, 2013 1474 /id}

REST-ON participants return to the clinic each week for routine follow up and assessment of treatment response, BP, and adverse events. If the patient and research physician judge the benefit of study drug to be inadequate for sleep continuity or nightmares, then the dose may be increased according to the titration schedule below. At any point during the medication titration, upward dosages will not be permitted if: systolic BP <90, or diastolic <50, either sitting or standing, or if the patient has felt faint or near-syncopal, or has had a syncopal attack. The final research visit will be at the end of the eighth week of randomized treatment, and decisions will be finalized at that time of transition to care as usual.

Table1 Prazosin dose titration schedule

Week/Day	Men's Dose	Women's Dose
Days 1-2	1	1
Days 3-7	2	2
Week 2	4	2
Week 3	6	4
Week 4	10	6
Week 5	15	10
Week 6	20	10

#### Calculating the number of study-drug capsules dispensed at each visit

At the time of the first medication dispensation, enough medication will be given to last until the next scheduled visit one-week later, plus three more days in case the visit has to be rescheduled. Thus, at the time of the first dispensation, participants will receive 2 capsules for the first two nights, then 10 capsules for the next 5 nights (in the even that there is inadequate effect from one capsule), then 6 more capsules for three more nights in the event that the one-week follow up must be rescheduled. This means that participants will receive 18 capsules at the time of the first dispensation.

Participants will be asked to bring all remaining study drug to the next visit to estimate adherence and medication usage rates. At the time of the second dispensation at the end of week-one of randomized care, participants will be eligible to increase the dose according to the titration schedule, with additional capsules

available in the event that the second follow up visit is later rescheduled up to three days past the one-week timeframe. Of course, the number of capsules will be less in the event that (1) a lower dosage was found to be effective in treating nightmares in the first week, or (2) there are side effects or hypotension at lower doses.

#### Randomization and blinding

Randomization of the 20 participants will be accomplished with blocked randomization: 5 blocks of two patients each. Blinding will be single blind, as the placebo we will use will be a generic lactose-filled capsule, and we will not attempt to create a matching placebo for the purposes of this pilot study. Our reasons for not making a matching placebo are as follows: (1) prazosin is generic and the physical appearance of the prazosin capsules may be subject to change, (2) the vast majority of participants will not know what generic prazosin looks like and hence will remain blind even if the placebo does not look like generic prazosin, (3) our most important outcome measures are self-report measures and hence not subject to investigator bias, (4) from prior experience, we have learned that creation of matching placebos would incur a minimum expense of about \$1000 - an expense that is unnecessary for our purposes.

#### Post-randomization care

Participants are referred for standard outpatient management at the end of 8 weeks of randomized care. The blind will be broken by a psychiatrist who is not involved in the patient's care during the study, and depending upon randomized assignment and the response to treatment under randomized assignment, the patient will then have the option of receiving a prazosin prescription at the end of the trial until they re-enter usual care. While study drug and doctor's visits were provided to the participants at no cost during randomization, the cost of medications and doctor's visits will be borne by the participant or their insurance company after they leave randomized care. Weekly phone calls will be made after the last visit until the patient has connected with their care provider.

#### 3.e.5. Measurement of Suicidal Ideation and Behavior

The Scale for Suicide Ideation (SSI) consists of 19 items that evaluate active suicidal desire, specific plans for suicide, and passive suicidal desire.{Beck, 1979 18 /id;Beck, 1997 19 /id;Beck, 1999 20 /id} Each item is rated by the patient on a 3-point scale from 0 to 2 for a maximum score of 38; a lower score indicates less severe suicidal ideation. The SSI will be collected at baseline and at weeks 1, 2, and 4 of randomized treatment, and once by telephone one month after completing randomized treatment. An SSI score >2 predicts increased risk for suicide death over a period of years.{Brown, 2000 314 /id} The SSI will be collected at the start of each visit, before the participant is seen by the study psychiatrist.

The Columbia-Suicide Severity Rating Scale (C-SSRS){Oquendo, 2003 1195 /id} is based upon the Columbia Classification Algorithm of Suicide Assessment(C-CASA).{Posner, 2007 932 /id} This C-SSRS is used by the FDA in clinical trials to assess suicide risk, and includes a structured assessment of past or recent suicidal behavior. It will be administered at each visit by a study psychiatrist blinded to treatment assignment. C-CASA has excellent inter-rater reliability in classifying suicide attempts, with an overall intra-class correlation coefficient of 0.89.

#### 3.e.6. Measurement of PTSD symptom severity

The severity of PTSD symptoms will be measured with the PTSD-checklist-specific version (PCL-S). The PCL-S has been shown to have excellent test-retest, internal consistency, convergent and discriminant validity (versus depression), and good sensitivity to change.{Wilkins, 2011 1382 /id} Each participant will complete this self-report scale.

#### 3.e.7. Measurement of Depression

Depression severity will be tracked by the observer-rated 24-item HRSD. {Hamilton, 1960 371 /id;Beck, 1988

337 /id} The HRSD24 will be administered by same project manager, blind to treatment assignment, at baseline and thereafter at weeks 1, 2, and 4 of randomized treatment. Research staff will demonstrate inter-rater reliability  $> 0.85$  against a criterion-set of clinical videotapes. The HRSD24 has three sleep items and one suicide item. The HRSD will be recorded as the total score (HRSD24), and will also be analyzed without the three sleep items or the suicide item (HRSD20). The three insomnia items and the suicide item will be separately examined.

### 3.e.8. Measurement of nightmares: The Disturbing Dreams and Nightmare Severity Scale

The frequency and intensity of disturbing dreams and nightmares will be measured with the Disturbing Dreams and Nightmare Severity Scale (DDNSI). This scale is derivative of a simpler Nightmare Frequency Questionnaire that had a test-retest weighted kappa  $> 0.85$ . {Krakow, 2002 813 /id} The revised DDNSI has good internal consistency with a Cohen's alpha  $> 0.80$ . {Bernert, 2005 798 /id; Bernert, 2009 1044 /id} A DDNSI score  $> 10$  indicates a clinical nightmare disorder. {Krakow, 2002 1368 /id} Each participant will complete this self-report scale.

### 3.e.9. Measurement of insomnia: The Insomnia Severity Index

The Insomnia Severity Index (ISI) is a 7-item self-report measure that examines the intensity of distress associated with night-time and daytime symptoms of insomnia. It is well validated and we have used it extensively in our own research. We have no a prior hypotheses regarding the ISI scale, but include it primarily to provide a complete description of sleep symptoms. {Bastien, 2001 639 /id}

### 3.e.10 Qualitative assessment of nightmares

The VAS scales are designed to tease out any important differences between depressing dreams as reported in depressed patients as opposed to classic PTSD-type nightmares. The VAS scales will be 100 mm long, and will be anchored to the left end with the word 'never', and anchored on the right end with the word 'always'. The participant will be asked to make a single mark on each of several VAS lines relevant to each of the following dimensions of their dreams:

- Repetitive sameness of the dream plot from night-to-night
- Dream content is related to prior real-life traumatic event
- Likelihood of awakening from the dream
- Feeling sad during or after the dream
- Feeling scared during or after the dream
- Feeling angry during or after the dream

### 3.e.11 Blood pressure measurement

Blood pressure will be measured at each REST-ON visit after 5 minutes of quiet sitting, followed by 2 minutes of standing. BP will be measured with an approved automated BP machine.

### 3.e.12 Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I)

The participants' overall clinical status and response to treatment will be assessed with the CGI-S and CGI-I. Both scales will be rated along a 7-point dimension. The CGI-S and CGI-I will be completed by a study psychiatrist. The CGI-S will be scored from "Normal" to "Among the most severely ill", while the CGI-S will be scored from "Very much improved" to "very much worse". The CGI-S will be completed at baseline and at all randomized treatment visits, while the CGI-I will be completed only during post-randomization treatment visits.

### 3.e.13. Salivary amylase

In humans,  $\alpha$ -amylase levels are highest in pancreatic and salivary secretions. Increased salivary amylase activity is a marker for increased sympathetic nervous system activity. {Nater, 2009 1466 /id} We will collect samples of saliva at baseline and each follow up visit. The tubes containing the samples will be vortexed, centrifuged at 2000xg at 4 C for 10 minutes, and the saliva will be aliquoted and frozen at -80C for future

analysis. On the day of the assay, the samples will be thawed and will be centrifuged once more to assure that solids are removed from suspension. Salivary amylase activity will be determined using the Amylase Activity Assay kit (Sigma). In this kit, amylase activity is determined using a coupled enzymatic assay, which results in

	Baseline of REST-ON	Follow up Visits in REST-ON	
Evaluation to sign consent	1		
Consent	2		
Registration	3		
Demographics	4		
Visual Analogue scales for nightmare descriptors	5		
Vitals with orthostatic BP	6	1	
PCL-S	7	2	
SCID and CAPS	8		
Hamilton Rating Scale for Depression (HRSD)	9	7	
Beck Suicide Severity Index (SSI)	10	3	
Columbia-Suicide Severity Rating Scale	11	4	
Disturbing Dreams and Nightmare Severity Index	12	5	
Insomnia Severity Index	13	6	
Concomitant Medications	14	8	
CGI-S	15	9	
CGI-I	16	10	
Adverse events		11	
Encounter Disposition Form- Baseline/Baseline Follow-up	17	12	
Study Medication Accountability		13	
Salivary amylase	18	14	
	Baseline of REST-ON	Follow up Visits in REST-ON	
Evaluation to sign consent	1		
Consent	2		
Registration	3		
Demographics	4		
Visual Analogue scales for nightmare descriptors	5		
Vitals with orthostatic BP	6	1	
PCL-S	7	2	
SCID and CAPS	8		
Hamilton Rating Scale for Depression (HRSD)	9	7	

Table 2 – Order of Assessments for REST-ON-PTSD

<b>Beck Suicide Severity Index (SSI)</b>	<b>10</b>	<b>3</b>
<b>Columbia-Suicide Severity Rating Scale</b>	<b>11</b>	<b>4</b>
<b>Disturbing Dreams and Nightmare Severity Index</b>	<b>12</b>	<b>5</b>
<b>Insomnia Severity Index</b>	<b>13</b>	<b>6</b>
<b>Concomitant Medications</b>	<b>14</b>	<b>8</b>
<b>CGI-S</b>	<b>15</b>	<b>9</b>
<b>CGI-I</b>	<b>16</b>	<b>10</b>
<b>Adverse events</b>		<b>11</b>
<b>Encounter Disposition Form- Baseline/Baseline Follow-up</b>	<b>17</b>	<b>12</b>
<b>Study Medication Accountability</b>		<b>13</b>
<b>Salivary amylase</b>	<b>18</b>	<b>14</b>

### 3.e.14 Adverse events

The study psychiatrist will elicit spontaneous reports of adverse events (AEs) and serious adverse events (SAEs) at each treatment visit. In the unexpected event of potentially self-injurious behavior, the behavior will be coded as a suicide attempt according to the Columbia-Suicide Severity Rating Scale (C-SSRS){Oquendo, 2003 1195 /id}, which in turn is based upon the Columbia Classification Algorithm of Suicide Assessment(C-CASA) {Posner, 2007 932 /id}. The C-CASA will be completed by the study psychiatrist and has excellent inter-rater reliability in classifying suicide attempts, with an overall intra-class correlation coefficient of 0.89.

## **STATISTICAL CONSIDERATIONS**

### 3.f. Statistical Analyses

Outcome measures will be collected at baseline and weekly for the 8 weeks of participation. Repeated measures models will be used to assess the changes over time in suicidal ideation and intensity of nightmares

and disturbing dreams. These models will be used to obtain estimates of the treatment effects (the changes in the outcome measure from baseline to end of randomization), estimates of the variability of the outcome measures at each time adjusted for baseline measures, and estimates of the within patient correlations over time. These estimates will be used in the design of a subsequent adequately-powered randomized clinical trial. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations to satisfy the 1) linearity, 2) homogeneity of variances, and 3) normality assumptions. While we assume compound symmetry for the correlation among repeated measures, we will also consider other covariance patterns. We will also assess the correlation amongst all the measures collected over time. While our sample size is small, we will also use a mediation analysis to determine the degree to which nightmares are responsible for (or mediate) the changes in suicidal ideation.{Baron, 1986 1126 /id}{MacKinnon, 2004 1260 /id;Efron, 1979 1261 /id}

### 3.g. Potential Pitfalls and Alternative Solutions

- Alternatives to Prazosin: Clonidine has been reported to have some effect in reducing nightmares but is generally described as less effective than prazosin. In contrast, prazosin is the best-practice pharmacologic treatment for nightmares is prazosin.{Aurora, 2010 1365 /id} Some psychotherapies that hold promise for the treatment of nightmares, notably imagery rehearsal therapy.{Hansen, 2013 1370 /id} However, this approach is unlikely to be adopted by most physicians managing PTSD. This approach may well prove to be useful but deserves its own separate line of inquiry.

### Conclusions and Future Directions

Results from this project will provide a first clue as to whether a SSRI-prazosin combination treatment is a candidate treatment for reducing the intensity of suicidal ideation in PTSD patients. If so, it opens the possibility that other forms of nightmare treatment (i.e., imagery rehearsal therapy) may also have benefit. This project will also provide support for hypothetical mechanisms explaining the association between nightmares and suicidal ideation.

## 6. PROTECTION OF HUMAN SUBJECTS

### 6.a Subject selection procedures

The subject selection features of REST-ON-PTSD are intended to: (1) yield a sample with PTSD associated with suicidality, and (2) exclude patients who might be harmed by exposure to psychotropics, including pregnant women. Three procedures are used to assure participant safety at the baseline assessment: the Mini Mental State Exam (MMSE),{Folstein, 1975 78 /id} a pregnancy test for women of conception age, and a baseline Columbia- Suicide Severity Rating Scale (C-SSRS) score.

A MMSE score < 24 is statistically abnormal at any age and is consistent with global cognitive deficits such as seen in dementia.{Crum, 1993 313 /id}

All women of child bearing age will complete a urine pregnancy test at the first face to face visit. Persons excluded because of overly intense suicidal ideation (C-SSRS suicidal ideation score >3) will be evaluated for safety and perhaps the need for psychiatric hospitalization.

The additional subject exclusion factors are:

- History of sensitivity or allergy to prazosin or quinazolines
- History of fainting or syncopal episodes in the last 6 months
- History of hypotension
- Automatic Blood Pressure readings with systolic BP <90, or diastolic <50, either sitting or standing.
- Planned use of sildenafil, tadalafil, or similar erectile dysfunction medication

### 6.b. Recruitment and Consent Procedures

#### 6.b.1. Recruitment

**6.b.2. Consent procedures** The Project Manager will describe the overall study design, and will detail the time commitment required from the participant. The project manager provides a copy of the consent form, allowing enough time for the participant to read the consent form and ask questions, and sign the consent form. We will assure the capacity of each patient to understand the risks and benefits of participation by assessing each participant with the Evaluation to Sign Consent (ESC). The ESC was developed by Love in 1988 (unpublished; as cited in Deronzo, Conley, & Love, 1998).{Deronzo, 1998 1446 /id} The ESC assesses the factual understanding of subjects, is composed of five items, and can be adapted to any research design.

### 6.c. Potential risks

The risks of participating in this project are related to prazosin. The primary risk from prazosin is orthostatic hypotension. Prazosin is an  $\alpha_1$  adrenergic receptor blocker approved for use as an antihypertensive. The cardiovascular effects of the drug were fully characterized more than 30 years ago.{Colucci, 1982 1369 /id} It generally has no effect on heart rate. The most common side effects at these doses in hypertensive patients are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. The most common side effects (>5%) when given to patients with PTSD are: lightheadedness 25%, nasal congestion 22%, and palpitations (6%).{Raskind, 2013 1474 /id} We will manage the risk of hypotension by excluding participants with a history of fainting or syncopal episodes in the last 6 months, history of hypotension, or automatic Blood Pressure readings with systolic BP <90, or diastolic <50, either sitting or standing. The risk of side effects might be severe if the patient took an intentional overdose,

although limited reports of overdose suggest a low acute toxicity.{Lip, 1995 1447 /id}

#### **6.d. Safeguards**

The Star\*D trial was among the first NIH-sponsored trials to follow the 2001 NIH guidelines for studies which included patients at risk of suicide. <http://www.nimh.nih.gov/health/topics/suicide-prevention/issues-to-consider-in-intervention-research-with-persons-at-high-risk-for-suicidality.shtml> {Nierenberg, 2004 924 /id} The guidelines have several stipulations, and we have responded accordingly:

- 1) "Provide specific inclusion criteria and their measurement with regards to suicidality"

Response: Patients included in the study will have a Scale for Suicidal Ideation (SSI) scores  $\geq 3$  but with C-SSRS suicidal ideation scores of  $\leq 3$ . This range defines patients with mild and moderate suicidal ideation, but with no intent to commit suicide. This inclusion range for suicidal ideation is consistent with prior clinical trials of suicidal patients. {Brown, 2005 1468 /id; Grunebaum, 2012 1470 /id}

"Specify the criteria for withdrawal from the treatment trial with regard to increased suicidality, increased related symptoms, lack of treatment response, and treatment side effects, and what alternative treatment or referral will be offered."

Response: The decision to withdraw the participant from research treatment will be based upon either the participant's view or the research psychiatrist's opinion that the patient is experiencing severe suffering, is at imminent risk for suicide, or is functionally decompensating. The clinician's opinion will be informed on the basis of the DDNSI, the PCL-S, and the C-SSRS, but the decision to withdraw a participant will be based upon a combination of psychometrics along with global clinical judgment. If a participant is withdrawn from the study, then he or she will be offered care-as-usual, or hospitalization if necessary.

- 2) "Consider and establish criteria for hospitalization, where the hospitalization will take place, and the procedures within the hospital that provide additional safety"

Response: Hospitalization will be offered if the patient is judged at imminent risk of suicide, is functionally decompensated, or needs specialized treatment outside of the protocol (such as ECT), according to the global clinical judgment of the study psychiatrist. Hospitalization would take place in the inpatient units of Georgia Regents Medical Center, or East Central Regional Hospital, or similar regional facility.

- 3) "Describe procedures in the protocol for managing increases in suicidality, and how research staff is trained and available to provide clinical management"

Response: Managing increases in suicidality is predicated upon detection of such increases. Although we proposed to examine participants weekly, we recognize that suicidal ideation may emerge suddenly and unpredictably. Therefore, research staff will make at least one mid-week phone call to each participant for the first 2 weeks to check on their well-being and assure them that the study staff is available. At each scheduled study visit, the protocol will quantify suicidality 2 ways. First, the participant will complete the

Scale for Suicide Ideation. This information flows from the research staff to study psychiatrists at the time of the visit. Second, the research psychiatrist will administer the Columbia Suicide Severity Rating Scale (C-SSRS), allowing for a thorough review for the presence of any self-injurious behavior since the last visit or the development of any preparatory suicidal planning, as categorized by the C-SSRS.{Oquendo, 2003 1195 /id} Patients judged by the study psychiatrist to be at increased risk of suicide will have an increased frequency of research visits, have smaller supplies of research medication, or may be withdrawn from the study and possibly hospitalized.

- 4) "Have a procedure for emergency coverage that is clearly understood by the clinical research staff, study participants, and families"

**Response:** At the time of consent, participants will receive clear instructions for how to reach study staff during the daytime, and how to access after-hours coverage as provided through each site. Psychiatry residents-in-training who receive emergency calls from participants after-hours will be instructed to call the local principal investigator immediately, regardless of the time of day. The PI or designated co-I will be continuously available to the respective on-call residents to guide crisis management and assess for the primary suicidal endpoints, if necessary by phone.

- 5) "As part of the consent process, consider having explicit discussion with relevant family members, guardians, or friends that includes the risks inherent when study participants are suicidal (risk of death, side effects of treatment)"

**Response:** Involvement of the participant's family will be encouraged, starting by asking potential participants to bring their families to the first face-to-face screening visit.

- 6) "Consider and identify the limits of confidentiality with respect to suicidality, as well as other circumstances"

**Response:** When a participant has emergent suicidality defined as an increase of 6-points (one standard deviation of SSI scores in Dr McCall's outpatients), we will inform the participant of our intent to share this with the relevant family, and the consent form will reflect this.

- 7) "Consider the impact of suicidality on the study participant's capacity to give informed consent"

**Response:** Consent will be obtained only from persons who normally would not meet criteria for emergent psychiatric hospitalization, i.e., C-SSRS suicidal ideation score < 4.

- 8) "Determine whether additional safeguards are needed to ensure the safety of the study participants"

**Response:** No additional safeguards needed

- 9) "Consider situations in which a trial would be terminated prematurely"

**Response:** As this is a pilot study with only 20 participants, we have no statistical endpoints for early termination of the study. However, the trial would be terminated prematurely only if the Medical Monitor determined that there was a systematic increase in risk, according to the Data Safety Monitoring Plan,

below.

#### **6.e. Data Safety Monitoring Plan**

Dr. Brian Miller of the Department of Psychiatry and Health Behavior will serve as the internal Medical Monitor for this study. Dr. Miller will have no other relationship with this study or any other study on which Dr. McCall is the principal investigator. All serious adverse events (SAEs) will be reported immediately to Dr. Miller. Otherwise Dr. Miller will review the case report forms for the Scale for Suicide Ideation, vital signs, and AEs after the third and sixth patients are completed.

#### **6.f. Confidentiality of subjects' responses**

All participants are assured of confidentiality of the information obtained during their participation, with the exception of the expression of imminent suicidality. We will make every attempt to secure the participant's permission to share a high risk of suicide with the participant's family. All participants are assigned a subject number for the internal purposes of the research, and the patients' identity on Case Report Forms is indicated only by their subject number and initials. Case Report Forms are locked in the research offices of the principal investigators. Original source documents relevant to the delivery of clinical care are kept in the patient file office of the Department of Psychiatry and Health Behavior which is continuously staffed or locked, and these clinic files do not circulate beyond the Department. Participants will be advised that confidentiality could be breached in the event of an audit by the parent institution or the sponsor.

#### **6.g. Research procedures**

Risks of teratogenicity will be limited by obtaining a pregnancy test from each women of childbearing potential before exposure to the first week of outpatient treatment and by counseling on the need for birth control. Pregnancy will be an exclusion criterion for study entry or for continued study participation. The research procedures include weekly assessment of suicidal ideation (the SSI and C-SSRS) and side effects related to medication. A study psychiatrist will examine each participant weekly during routine study visits and will clinically assess the risk of suicide. Participants judged to be at imminent risk of suicide will be managed as described above. Participants will only be given enough study medication to last until their next research visit. The principal investigators or designated co-Is will be available 24-hours per day by phone and beeper in the event of a participant's medical emergency for the entire duration of the trial. Subjects will be provided with a business sized card to carry in their wallets. This card will include contact information for the physicians and staff members. In addition, it will include a 24-hour number to call in case of emergency. This number will put the subject in touch with the Resident-On-Call provided by the Departments of Psychiatry and Health Behavior. The Resident will be able to put the subject in touch with the PI if needed.

#### **6.h. Risk/benefit ratio**

##### **6.h.1. Risks**

Emergent suicidal ideation or behavior is a risk of mental disorders. We have operationalized emergent suicidal ideation as a 6-point increase. These risks will be discussed with the participant as part of the consent process. The risk of a fatal outcome from a suicide attempt is mitigated by limiting access to study medication. The likelihood of side effects related to prazosin is primarily hypotension and fainting. The risk of side effects might be severe if the patient took an intentional overdose, although limited reports of overdose suggest a low acute toxicity.<sup>{Lip, 1995 1447 /id}</sup> Mechanisms will be in place to mitigate suicide risk.

### **6.h.2. Benefits**

Benefits of participation include nightmare treatment at no cost to the patient. Treatment of nightmares should bring lessened psychic distress and perhaps lessen suicidal risk. The frequency and intensity of patient monitoring for suicidal thinking is greater than that seen in routine care, and is an additional benefit. The overall benefit/risk ratio in this clinical trial is highly favorable, with a large potential impact upon public health policy in the management of depression with insomnia.

### **6.i Gender and minority recruitment**

It is expected that women will constitute approximately 50% of the sample, since women represent both the majority of persons suffering with either depression or insomnia. Minorities, chiefly African-Americans, will comprise approximately 15% of the total sample.

**6.j Targeted/Planned Enrollment**

**Table 3.**  
**Targeted/Planned Enrollment**

<b>TARGETED/PLANNED ENROLLMENT: Number of Subjects</b>			
<b>Ethnic Category</b>	<b>Sex/Gender</b>		
	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	0		0
Not Hispanic or Latino	12	6	18
Ethnic Category Total of All Subjects*	12	6	18
<b>Racial Categories</b>			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	2
White	12	6	18
Racial Categories: Total of All Subjects *	14	6	20

**6.k. Children and adolescents**

Children under 18 years old will be excluded since the safety of prazosin for nightmares has not been examined.

**7. Vertebrate Animals      N/A**

