PENNSTATE

HRP-591 - Protocol for Human Subject Research

Protocol Title: ***Effectiveness of Prazosin in Bulimic patients experiencing nightmares due to PTSD***

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1.0 Objectives

1.1 Study Objectives

The **aim** of our study is to evaluate the effectiveness of prazosin in bulimic patients experiencing distressing nightmares secondary to PTSD. We will be testing 10 participants. 8 will be tested using subjective measures (Phase A). If a signal of efficacy is detected the last 2 participants will be tested using additional objective PSG measurements (Phase B). Phase B will be a feasibility study and based on results PI will apply for external funding.

AIMS FOR PHASE A:

The **Primary aim** of our study is to evaluate the effectiveness of prazosin in bulimic patients experiencing distressing nightmares secondary to PTSD using subjective measures.

Hypothesis 1:
Prazosin is associated with decrease in nightmare frequency in bulimic patients

The **secondary aim** of our study is to assess changes in Cortisol levels in bulimic patients with PTSD before and after treatment with prazosin.

Hypothesis 2:
Prazosin use is associated with a decrease of cortisol levels.

1.2 Primary Study Endpoints

Primary outcome measure: Decrease in frequency of nightmares (subjective measures)

1.3 Secondary Study Endpoints

Secondary Outcome measures: Decrease in total CAPS score, depressed mood, bulimia symptoms and self-harm thoughts on depression scale

AIMS FOR PHASE B:
Phase B will involve using objective polysomnogram measurements (hypothesis 3) in addition to the subjective instruments used in phase A.
The **Primary aim** of our study is to evaluate the effectiveness of prazosin in bulimic patients experiencing distressing nightmares secondary to PTSD using subjective measures.

Hypothesis 1:
Prazosin is associated with decrease in nightmare frequency in bulimic patients

The **secondary aim** of our study is to assess changes in Cortisol levels in bulimic patients with PTSD before and after treatment with prazosin

Hypothesis 2:
Prazosin use is associated with a decrease of cortisol levels.

Hypothesis 3:
Prazosin is associated with decrease in REM density & normalization of REM disruption (objective).

1.4 Primary Study Endpoints

Primary outcome measure: Decrease in frequency of nightmares (subjective measures)
Decrease in REM density on PSG (objective measures)

1.5 Secondary Study Endpoints

Secondary Outcome measures: Decrease in total CAPS score, depressed mood, bulimia symptoms and self-harm thoughts on depression scale

2.0 Background

2.1 Scientific Background and Gaps

Nightmares are a frequent and distressing symptom in patients struggling with post-traumatic stress disorder (PTSD). Up to eighty percent of patients with PTSD experience nightmares which predominantly occur during the REM phase of sleep[1]. Some adult studies have also demonstrated association between suicidal ideation or attempt and increased REM sleep[2]. PTSD presents as common comorbidity with eating disorders and traumatic experiences often lead to development of Bulimia nervosa[3]. According to some studies up to 40 % of women with bulimia nervosa experience PTSD and the frequency is even higher in those with active binging symptoms[3, 4].

2.2 Previous Data

PTSD has been associated with the etiology, course, and severity of Bulimia nervosa[3]. Nightmares are frequently reported by patients struggling with bulimia nervosa & PTSD. Clinicians managing patients with bulimia nervosa frequently report that bulimic patients experiencing nightmares have more serious psychopathology. However, little is known about the impact of nightmares on the severity and course of bulimia. Some researchers have posited that treatment resistance in bulimic patients may be secondary to PTSD symptomatology and treatment of PTSD may alleviate bulimic symptoms[5]. However, no studies have explored the impact of nightmares on bulimic symptoms, and whether their presence predicts the course or treatment response in bulimia nervosa. This gap in our knowledge is crucial given the high frequency of PTSD symptoms in bulimia.

Deregulated hypothalamic-pituitary-adrenal axis activity has been reported in both PTSD and Bulimia nervosa but the results of the studies are inconsistent. Some studies in PTSD report hypocortisolism at baseline[6, 7] while others report that women with higher cortisol responsiveness to stressors tend to eat more during stress. Furthermore, binging and purging symptoms may trigger increased release of cortisol accounting for high cortisol levels in many patients with Bulimia nervosa. Prazosin, an alpha-1 adrenergic receptor antagonist, affects the stress system, including HPA axis. Evaluating the activity of the HPA axis in bulimic patients with PTSD before and after treatment may help us understand the underlying pathophysiology of this disorder and in predicting treatment response in these patients[8].

Although various psychopharmacological options are being utilized to provide symptomatic relief of nightmares, there is limited scientific evidence about their effectiveness in nightmare management. Furthermore, literature is almost non-existent about therapeutic options for patients with bulimia nervosa experiencing nightmares. Prazosin has been used extensively for treatment of nightmares in PTSD in both civilian and veteran population and has proven to be subjectively and objectively effective[9, 10]. Reversal of REM sleep disruption has been observed following treatment with prazosin[11]. Other studies have reported decrease in trauma-related distressing dreams with the use of prazosin, which tend to return after its discontinuation[11].

2.3 Study Rationale

To our knowledge, there is no treatment trial for prazosin use in patients with bulimia nervosa struggling with nightmares, looking at either objective or subjective measures. We plan to probe the effectiveness of prazosin in bulimic patients experiencing nightmares due to PTSD using both subjective and objective measures in order to improve future clinical care. The effects of

prazosin on decreasing nightmares and bulimic symptoms on subjective scales and effects on sleep architecture using objective polysomnogram measurements will help inform targeted psychopharmacologic and psychotherapeutic strategies to improve clinical care of bulimic patients struggling with distressing dreams secondary to PTSD. This study will be performed in two phases. Phase A will involve eight participants who will be tested using subjective scales (mentioned below). If Phase A data analysis leads to detection of a signal of efficacy 2 more participants will be recruited to participate in phase B of this trial using objective polysomnogram measurements. The results from this project will aid in establishing a fully powered clinical trial for treatment of nightmares in bulimic patients and improve outcomes in this high risk population.

3.0 Inclusion and Exclusion Criteria

3.1 **Inclusion criteria**: Women struggling with bulimia nervosa (purging and non-purging type) between 18-45 years of age recruited via physician referrals or advertisement materials with complaints of nightmares secondary to PTSD. Patients may or may not be taking SSRIs and their use will not exclude them from the study.

3.2 **Exclusion criteria:** Restless leg syndrome, narcolepsy, sleep apnea, currently taking prazosin, neurological disorders, pregnancy, cardiac abnormalities, significant electrolyte abnormalities, use of steroids or Beta blockers and abuse of alcohol or other substance during the past three months(due to their effects on sleep parameters). Prazosin is commonly used to treat symptoms of PTSD and unless cardiac abnormalities are detected at baseline, EKGs are not routinely performed during treatment. We will exclude the patients with cardiac abnormalities from our study if the baseline EKG detects some abnormalities; they will be referred to cardiologist for further follow up. Blood work will be drawn to detect electrolyte abnormalities commonly seen in bulimic patients and patients will clinically significant electrolyte abnormalities will be excluded from the study. Physical examinations will not be performed as these patients follow up at the eating disorder clinic and those data are already available, data from the preexisting medical evaluations will be used to discern any major neurological or other physical abnormalities and participants will be excluded from the study.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Safety concerns, failure of subject to adhere to protocol requirements, subject consent withdrawal.

3.3.2 Follow-up for withdrawn subjects

A follow up phone call by the research assistant to provide instructions regarding the medication will be conducted. Patients will be asked to return any unused medication and standard care will be offered to patients if they choose not to participate in the research study or are withdrawn early.

4.0 Recruitment Methods

4.1 Identification of subjects

Subjects will be identified at the Briarcrest eating disorder clinic by a therapist & additionally there will be flyers in the office regarding participation in the study. Study flyers will also be sent to other physicians and therapists in the community. The therapist will screen and identify each subject and obtain verbal consent. After the initial screening, the therapist will inform the RA who will initially get verbal consent and schedule patient for the first day of screening procedures. The physical location of the evaluations will be at GCRC where the psychiatrist will perform the evaluations; however the initial screening by the therapist will take place at the Briarcrest eating disorder clinic.

4.2 Recruitment process

The research assistant will contact the participants to obtain consent and avoid any form of coercion from healthcare providers. The research assistant will get verbal consent via phone and schedule the patient for consent discussion, therapist evaluation (if not already in medical record), the screening lab work, pregnancy test, Salivary Cortisol collection, BMI, Vital signs, CMP, LFTs, UDS & EKG.

Informed consent will be obtained at the GCRC by the Research Assistant.

4.3 Recruitment materials

There will be flyers in the therapist office.

4.4 Eligibility/screening of subjects

The potential subjects will be patients following up in the eating disorder clinic. They will receive initial screening from the therapist who will use the DSM-5 based evaluation that is utilized routinely in the clinic and ascertain the diagnosis of Bulimia nervosa. Patients with co-morbid PTSD with ongoing nightmares (scoring 3 or above on distressing dreams item of the clinician administered PTSD scale (CAP) will be eligible for this study and the therapist will ask the patients whether they would like to be contacted by the research assistant to participate in the study.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

The consent process will take place in the GCRC before any study related procedures take place.

5.1.1.2 Coercion or Undue Influence during Consent

The PI or therapist providing care to the patient will not be involved in the consent process. The therapist will ask the

patient about their interest in participation in the study and whether they would like to be contacted by the research assistant. The research assistant will explore interest in participation via phone call and later on the written consent from participating subjects will be obtained at the time of the first blood draw. It will be emphasized that subjects do not have to participate. They will also be told that whatever their decision, their current and future care will not be affected.

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

A member of the research team authorized to carry out the consent process will:

1. Verify that the subject has received a copy of the consent form and had time to review it.
2. Review the consent form with the subject, answering any questions he/she may have.
3. Ask the subject to sign the consent form indicting he/she understands and agrees to study procedures before study procedures begin.
4. Obtain Signatures and give a signed copy of the consent form to the participant for his/her personal records.

5.2.2 Waiver of Documentation of Consent

N/A

Consent – Other Considerations

Non-English Speaking Subjects
N/A

5.2.3 Cognitively Impaired Adults

N/A

5.2.3.1 Capability of Providing Consent

The patients will be adults and will have the capacity to provide consent.

5.2.3.2 Adults Unable To Consent

N/A

5.2.3.3 Assent

N/A

5.2.4 Subjects who are not yet adults (infants, children, teenagers)

5.2.4.1 Parental Permission

N/A

5.2.4.2 Assent

N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☒ Authorization will be obtained and documented as part of the consent process.

☐ Partial waiver is requested for recruitment purposes only *(Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained)*

☐ Full waiver is requested for entire research study *(e.g., medical record review studies)*

☐ Alteration is requested to waive requirement for written documentation of authorization

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

N/A

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

6.2.2 Explanation for why the research could not be practicably be conducted without access to and use of PHI

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

6.3 Waiver or alteration of authorization statements of agreement

7.0 Study Design and Procedures

7.1 Study Design

Study Design: We plan to conduct a 7 week prospective, double blind, placebo controlled crossover study. Each patient, in a randomized design will receive three weeks of prazosin and three weeks of placebo separated by 1 week washout period. A 1-week washout period is considered sufficient, given that the half-life of prazosin is 2-3 hours, and previous studies have demonstrated that the clinical effects of prazosin are eliminated within a week[10, 11]. The subjects

will be blinded and the randomization list will be sent directly to the research pharmacy. Methylcellulose will be used as placebo.

7.2 Study Procedures (PHASE A)

- Subjective Scales: EDI-3 (eating pathology), PCL –C (PTSD checklist- civilian version), CAPS (Clinician administered PTSD scale), PSQI (Pittsburg sleep quality index), HDRS (Hamilton Depression Rating Scale) & 5 relevant questions from sleep-50 questionnaire.
- Other parameters: Salivary Cortisol (5 diurnal samples), BMI, Vital signs, EKG, CMP, LFTs, UDS. Saliva samples will be analyzed in our departmental lab using ELISA kits (Alpco). Blood samples will be sent to Quest Diagnostics Lab for analysis. The Biological Safety and Recombinant DNA Committee registration number is FUM15-01p-2.
- Upon completion of the intervention period, participants will return to the Milton S. Hershey Medical Center and repeat the exact same procedures as completed during the Baseline period including the vital sign measurements, blood, urine, & saliva collection, sleep lab recordings, and questionnaire completion. Any unused medication and/or the empty medication bottle will be collected at the end of both interventions.

7.2.1 Day 1

The first day of the study will involve Consent, standard evaluation by therapist, if not done previously, initial blood draw, urine pregnancy test and EKG. Patients will be referred to cardiologist, if needed based on EKG results and will be excluded from the study.

7.2.2 Day 2

On the second day of the study participants meeting eligibility criteria based on EKG & labs, will be assessed by the psychiatrist and 5 diurnal salivary samples will be collected from the participants. Patients will be randomly assigned to one of the treatment arms. The two treatment arms with Prazosin and Placebo will be monitored similarly. Rating scales will also be collected by RA that day at baseline, as well as on the last day of the first and second treatment arms and the last day of washout period (Total 4 times). Vital signs will be checked that day and on each physician visit. Prazosin will be prescribed by the PI (psychiatrist) at 1 mg (taken by mouth once or divided BID) after the initial assessment on the second day of the study.

7.2.3 Weekly Visits

Symptoms will be reassessed and medication will be adjusted by 1-2 mg increments every 7 days based on clinical response and severity of night mares, to achieve maximum therapeutic benefit while monitoring adverse effects using side effects scale on weekly basis (psychiatrist will be using the scale at every visit). A phone contact by RA will be made on the morning after dose initiation and after each increment to monitor adverse events. The end point for capping the Prazosin dose will be 6 mg daily. The psychiatrist will administer adverse events rating scale and nightmare assessment using Sleep-50 Questionnaire at every psychopharmacologic

visit after initiation of medication in addition to the initial visit. Vital signs will be checked at each visit as well. The participants will have a total of 7 visits with the psychiatrist (1 for initial evaluation and 3 for the dose titration during each study arm). Research pharmacy and RA will determine and track the sequence and random allocation of the medication to ensure blind randomized trial. RA will also gather salivary samples from the patient at end of each study arm (5 diurnal samples for each arm) After 3 weeks on one treatment arm, a wash out period of 1 week will be given prior to starting the second study arm. The same sequence will be repeated for the second study arm and study questionnaires will be repeated on the last day of the washout period. Blood work will be drawn thrice, once at baseline and once at the end of each study arm. 5 Diurnal salivary samples will be collected thrice, once at baseline and once at the end of each study arm. All sets of cortisol level will be collected at the same time points as the baseline level to allow accurate comparisons. All Rating scales will be completed 4 times, once at baseline, once at end of wash out period and once at the end of each study arm. At the end of each study arm, any unused medication will be collected from the participant. Upon completion of the study, participants may want to continue taking the study medication if they experienced positive results. The PI will discuss with each participant if it is appropriate to continue taking the medication.

Study Procedures (PHASE B)

Objective Measure: PSG (Polysomnogram) will be conducted at baseline for 3 consecutive nights and the last 3 nights of each treatment arm for a total of 9 nights/ person during Phase B of the study. 2 participants will be enrolled in this phase. All other procedures will be the same as described under Phase A.

7.3 Duration of Participation

The study duration is 7 weeks.

Phase A (No PSG Recordings)

			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Screening	Consent		x						
	Blood Collection, Urine Pregnancy Test, &EKG		x						
	Standard Evaluation by Therapist		x						
Baseline Procedures	Psychiatric Assessment & Randomization			x					
	Saliva Collection (8a, 12p, 3p, 6p, 9p)			x					
	Rating Scales (RS) and Vitals			x					
	Start Treatment			x					
Intervention Arm 1	Week 1	**Psychiatrist Visit**	x						
		Vitals, Adverse Event Rating Scale (AERS), Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 2	**Psychiatrist Visit**	x						

		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 3	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
		Saliva/Blood Collection & RS							x
Washout	Week 4	Rating Scales							x
Intervention Arm 2	Week 5	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 6	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 7	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
		Saliva/Blood Collection & RS							x

Phase B (2 subjects have PSG Recordings)

			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Screening	Consent		x						
	Blood Collection, Urine Pregnancy Test, &EKG		x						
	PSG Recording				x				
	Standard Evaluation by Therapist		x						
Baseline Procedures	Psychiatric Assessment & Randomization			x					
	Saliva Collection (8a, 12p, 3p, 6p, 9p)			x					
	Rating Scales (RS) and Vitals			x					
	PSG Recordings					x	x		
	Start Treatment							x	
Intervention Arm 1	Week 1	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 2	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 3	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
		Saliva/Blood Collection & RS							x
		PSG Recordings					x	x	x
Washout	Week 4	Rating Scales							x
Intervention Arm 2	Week 5	**Psychiatrist Visit**	x						

		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 6	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
	Week 7	**Psychiatrist Visit**	x						
		Vitals, AERS, Sleep-50	x						
		Research Assistant Phone Call		x					
		Saliva/Blood Collection & RS							x
		PSG Recordings					x	x	x

8.0 Data and Specimen Banking For Future Undetermined Research

N/A

8.1 Data and/or specimens being stored

8.2 Location of storage

Duration of storage

8.3 Access to data and/or specimens

.

8.4 Procedures to release data or specimens

8.5 Process for returning results

9.0 Statistical Plan (Phase A)

9.1 Sample size determination

Statistical Plan & Sample size determination

Power Calculation: Our plan is to recruit 10 patients with Bulimia nervosa and PTSD in this trial. Here we show our power calculations for the Hypothesis 1 and 2 based on our best knowledge. It should be noted that we assume no carry-over therapeutic effect in the calculation (see **Study Design**).

We choose the CAPS distressing dream item as the primary measure of nightmare frequency. Based on previous studies in similar patient populations, we assume the baseline nightmare score equals to 6.5, regardless of the treatment period. We anticipate the mean (SD) nightmare score of 6.0 (1.5) after being administered placebo for 3 weeks, and the endpoint mean (SD) for after be treated with Prazosin would reduce to 3.5 (2.5). We assumed that the correlation between two scores for the same patient equals to 0.3. With a sample size of 10 patients, we will have 80% power to detect the treatment effect, at 2-sided alpha level of 0.05. Other scenarios are presented in the table below.

CAPS Nightmare score			Correlation coefficient	Power
Baseline	Placebo	Prazosin		
6.5	6.0 (1.5)	3.5 (2.5)	0.3	80%
6.5	6.0 (1.5)	3.5 (2.5)	0.4	85%
6.5	6.5 (1.5)	3.5 (2.5)	0.3	92%
6.5	6.5 (1.5)	3.5 (2.5)	0.4	95%
6.5	6.5 (1.5)	4.0 (2.5)	0.3	81%
6.5	6.5 (1.5)	4.0 (2.5)	0.4	85%

9.2 Statistical methods

Statistical methods

The initial analyses of the data will include univariate exploration of all variables, using histograms, statistical summaries, and other graphical techniques. Expected ranges for all of the variables will be defined a priori, and out of range values, or values identified as outliers will be checked for errors, including going back to the original data forms. In addition to data cleaning, this initial analysis will serve the purpose of describing the patients' characteristics.
Our main objective is to identify the treatment effect. We hypothesize that there will be a reduction in cortisol levels and other subjective scores after being treated with Prazosin, whereas no significant change after being administered with placebo. To examine the treatment effect, both univariate and multivariable methods will be used. The analytic plan for hypothesis 1 and 2 will be similar, except the outcome measurements.
Univariate: T-tests will be used to analysis the mean difference of nightmare score, cortisol level, and other subjective scores.

Multivariable regression model: The mixed effects model will be used to examine the differences of the objective measures and subjective scores between two treatment arms. In these models, we will account for the period effect (period 1 or 2) and sequence effect (sequence Placebo-Prazosin or Prazosin-Placebo). The sequence effect will be treated as a random effect. Demographic characteristics and baseline measures will be treated as confounders and adjusted in the models as well. We expect no significant differences in the outcome variables will be observed between baseline and placebo. Therefore, the analysis will focus on the Prazosin vs. Placebo. Least squares mean, standard error of the mean, and p value for the differences will be presented as the final results.

Statistical Plan (Phase B)
Protocol B is only a feasibility study using 2 subjects therefore statistical support is not required.

10.0 Confidentiality, Privacy and Data Management

10.1 Confidentiality

10.1.1 Identifiers associated with data and/or specimens

Participant names, addresses, telephone/fax numbers, email addresses, date of birth, medical record numbers, social security numbers, etc. can be collected as part of this research study. All study data will be identified only by a code number rather than a name. The list linking the code number with any of the other identifiers is password protected and limited staff has access to it. Social security numbers are collected only for payment purposes and will not be stored after payment check is issued to the participant.

10.1.1.1 Use of Codes, Master List

All data will be identified only by a code number rather than a name. The list linking the code number to any other identifiers is stored in a password protected database, located on the Department of Psychiatry private network.

10.1.2 Storage of Data and/or Specimens

Paper files are stored in a locked filing cabinet in C5600D. Electronic data is stored on the Psychiatry server (Microsoft Server 2003) with active directory limiting access established by the Primary Investigator.

10.1.3 Access to Data and/or Specimens

Only the PI and 1-2 key research team members have access to the data/specimens.

10.1.4 Transferring Data and/or Specimens

N/A

10.2 Privacy

The research team has access only to information about the subjects provided by the subject during the research study. The Department of Psychiatry is extremely concerned about all issues related to privacy and confidentiality and is experienced in procedures of maintaining it effectively.

All study procedures including phone conversations, obtaining consent, and clinic visits will be conducted in private offices or exam rooms within the General Clinical Research Center. Participants are volunteers and may discontinue the research procedures at any time with no penalty or loss of benefits to which they are entitled.

11.0 Data and Safety Monitoring Plan

Although prazosin is routinely used in clinical settings in bulimic patients experiencing PTSD and nightmares and thus does not pose more than minimal risk for the patients, the research team will have the following data and safety monitoring plan to ensure safety and prevent any untoward outcomes.

11.1 Periodic evaluation of data

Subjects will be monitored weekly by a board certified psychiatrist to evaluate safety. The PI and co-investigators will be looking at the date monthly to further ensure safety of subjects.

11.2 Data that are reviewed

Vital signs, lab work, side effects and scales of symptom severity will be reviewed periodically to ensure safety.

11.3 Method of collection of safety information

The information will be collected at study visits and if needed, follow up phone calls will also be used.

11.4 Frequency of data collection

Data collection will be as described in the methods and recruitment section. Vital signs will be collected at every visit; similarly adverse events will be monitored on a weekly basis. Scales of symptom severity will be collected 4 times during the duration of the study.

11.5 Individual's reviewing the data

The data will be reviewed by PI and co-investigators, the findings will be reported to the IRB by PI.

11.6 Frequency of review of cumulative data

Monthly reviews of the data will be conducted

11.7 Statistical tests

N/A

11.8 Suspension of research

Any life threatening adverse events or outcomes endangering subject safety will trigger immediate suspension of research.

12.0 Risks

There may be discomfort associated with removing blood by venipuncture (by needle from a vein). A slight pinch or pin prick may be felt when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

There is no risk involved with the collection of saliva for diurnal cortisol testing.

There is a minimal risk associated with the discomfort of having standard clinical EEG paste electrodes applied to the scalp and EKG Stickers applied to the chest when performing polysomnography. Rarely, we have had an individual who has had a mild allergic reaction to the tape applied over electrodes. This risk is minimized by using hypoallergenic tape. If a sleep disorder is discovered, the participant will be referred to a sleep specialist or family doctor for further follow up as needed.

There is no risk or real discomfort associated with an EKG, however body hair can sometimes interfere with the signal recording and at times a small patch of hair may need to be shaved in order to place the electrode. Abnormal findings will be reviewed by a physician and referred to cardiologist for further follow up, if needed.

There is a risk of loss of confidentiality if medical information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

The most common side effect of low-dose Prazosin when administered at bedtime may cause orthostatic hypotension especially after first dose. Other common side effects of Prazosin include palpitations, headache, dry mouth, blurred vision, dizziness, fatigue, constipation, diarrhea and nausea.

The risks to an unborn baby or a nursing child from the study drug are largely unknown, though some animal studies suggest adverse events. Limited use in pregnant women has not demonstrated any fetal abnormalities or adverse events. Women who are pregnant or are nursing a child may not participate in this research study. Participant must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation. The investigator will discuss appropriate precautions with participant. If at any point during the research participant believes there is any possibility of pregnancy, they must notify the investigator immediately.

When participants are in the group that receives placebo, their condition will go without active treatment for three weeks in addition to the one-week washout period and their symptoms may get worse.

13.0 Potential Benefits to Subjects and Others

13.1 Potential Benefits to Subjects

The subjects will have no direct benefits. During the active treatment arm, symptoms may get better.

13.2 Potential Benefits to Others

There is no previous study demonstrating the benefits of the Prazosin use in Bulimic patients for treatment of night mares related to PTSD. This project will provide insight into the effectiveness of this medication and aims to decrease the distress associated with nightmares.

14.0 Sharing Results with Subjects

The individual results will not be shared with the subjects or their healthcare providers. If a condition is discovered, the participant will be referred to their family physician for appropriate follow up care.

15.0 Economic Burden to Subjects

15.1 Costs

N/A

15.2 Compensation for research-related injury

The research involves no more than minimal risk to subjects that they may incur as part of routine treatment with Prazosin. It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research–related injuries will be charged to subjects or their insurance carriers.

16.0 Number of Subjects

Subjects: 15 patients will be identified and screened for participation in the study. Only 10 patients with Bulimia nervosa and PTSD will complete the study and be included in the final analysis. The additional 5 participants will allow for screen failures or participant withdrawal after consent is obtained. This sample size has been derived from the previous studies in PTSD that have investigated the role of Prazosin in alleviating nightmares and other PTSD symptoms.

17.0 Resources Available

17.1 Facilities and locations

Briarcrest Clinic & GCRC– For recruitment and enrollment as well as follow up with psychiatrist to monitor symptoms.

17.2 Feasibility of recruiting the required number of subjects

The potential subjects are the patients who already follow up with the eating disorders clinic; the therapist will screen all patients following up with her for potential suitability to participate in the study until the proposed number of subjects has been recruited.

17.3 PI Time devoted to conducting the research

PI will devote 10% of time to this project to ensure that it is completed in the projected time frame. 1% of this time will be unfunded effort supported by Psychiatry.

17.4 Availability of medical or psychological resources

A therapist will be available for the assessment and screening as well as providing routine support for any ongoing issues. A referral to cardiologist will be made for any patients where cardiac assessment is indicated to ensure the cardiac stability of these patients.

17.5 Process for informing Study Team

The PI will meet with each team member separately to inform them of their expected participation and duties. The PI will also send a copy of the written protocol after IRB approval to each team member to ensure accurate understanding of procedures and will be available to answer questions by the research team.

18.0 Other Approvals

Approval from the departmental review committee and GCRC advisory committee will be obtained.

19.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subjects will be paid $500 for participation in the 7 week study. The 2 subjects who also participate in phase 2 (Protocol B) will receive an additional $500.

20.0 Multi-Site Research

20.1 Communication Plans

N/A

20.2 Data Submission and Security Plan

20.3 Subject Enrollment

20.4 Reporting of Adverse Events and New Information

20.5 Audit and Monitoring Plans

21.0 Adverse Event Reporting

21.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

22.0 Study Monitoring, Auditing and Inspecting

22.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

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24.0 Appendix

24.1 Test Article(s) (Study Drug(s) and/or Study Device(s))

24.1.1 Description

Prazosin is an FDA approved medication indicated for the treatment of hypertension. A common off-label use of the medication is PTSD-related nightmares and sleep disruptions. Prazosin is supplied in capsule form.

24.1.2 Treatment Regimen

In this study, prazosin capsules and placebo capsules will used for 3 weeks each. Capsules are taken by mouth at bedtime. The starting dose will be 1 mg and titrated by 1-2 mg each week as needed to achieve maximum therapeutic benefit while monitoring any adverse effects.

24.1.3 Method for Assigning Subject to Treatment Groups

All subjects will receive prazosin and placebo as a treatment at separate intervals during the study. The randomization process will determine which subjects receive prazosin first and which subjects will receive placebo first. We will use computer generated random numbers for randomization process.

24.1.4 Subject Compliance Monitoring

Subjects will be see by the psychiatrist each week during the study duration and will be asked to bring along their pill bottle so any remaining capsules can be counted and collected. The research assistant will also call the participants after each dosage increase to inquire about usage and side effects.

24.1.5 Blinding of the Test Article

The research pharmacy will provide the drug capsules which will be over encapsulated to maintain the same size as the capsules containing placebo.

24.1.6 Receiving, Storage, Dispensing and Return

24.1.6.1 Receipt of Test Article

We will obtain the drug and placebo from the Research Pharmacy.

24.1.6.2 Storage

The Research Pharmacy will store the drug and placebo according to their standard practice.

24.1.6.3 Preparation and Dispensing

Both the medication and placebo will be prepared by the Research Pharmacist experienced in drug research studies. The drug capsules will contain 1 mg prazosin and will be over encapsulated. Methylcellulose will be used in the placebo capsules.

24.1.6.4 Return or Destruction of the Test Article

At the conclusion of each study arm, the participant will return their pill bottle, so that any remaining capsules can be counted and collected and will be destroyed on site.

24.1.6.5 Prior and Concomitant Therapy

Prazosin is the only treatment being offered in this study. Subjects cannot be taking steroids or beta blockers and will be excluded from the study if used.