Cover Page for ClinicalTrials.gov

Official Title of the Study:

Combined Treatment of Prolonged Exposure and Pramipexole for Posttraumatic Stress Disorder and Depression

NCT Number:

NCT03765138

Principal Investigator:

Yuval Neria, PhD

Yuval.Neria@nyspi.columbia.edu

646-774-8041

Date of Document:

August 28, 2018

Statistical Analysis Plan

No statistical data will be produced due to early termination of protocol.

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

December 18, 2018

TO: YUVAL Y. NERIA, PHD

FROM: Dr. Edward Nunes, Co-Chair, IRB

Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: EXPEDITED APPROVAL OF PROTOCOL AMENDMENT

The amendment to your protocol #7692 entitled: COMBINED PROLONGED EXPOSURE AND PRAMIPEXOLE TREATMENT FOR PATIENTS WITH PTSD AND DEPRESSION **(to add exclusion criterion for attention allocation task only of current or past ADHD diagnosis; to add RecruitMe as a source of recruitment, as per the 12/14/2018 memorandum)** has been approved by the Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board.

Please note that this does not change the IRB's cycle of review. A progress report and an application for continuing review will be required 2 months before the study's approval is due to expire: (9/16/2019).

Signed copy on file at IRB.
EN/AHW/SCR4ALW

Protocol Title:
Combined Prolonged Exposure and Pramipexole Treatment for Patients with PTSD and Depression

Version Date:
12/18/2018

Protocol Number:
7692

Clinic:
Anxiety Disorders Clinic

First Approval:
10/04/2018

Expiration Date:
09/16/2019

Contact Principal Investigator:
Yuval Neria, PHD
Email: ny126@columbia.edu
Telephone: 646-774-8092

Co-Investigator(s):
Raphael Campeas, MD
Franklin Schneier, MD
Xi Zhu
Amit Lazarov

Research Chief:
Helen Simpson, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am proposing an amendment only to an existing protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Anxiety, Mood, Eating and Related Disorders
Within the division/department, what Center or group are you affiliated with, if any?
Anxiety Disorders Clinic

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
There are no investigators who will be participating in this protocol who are not affiliated with the New York State Psychiatric Institute or Columbia University.

Amendment

Describe the change(s) being made

We would like to add the following exclusionary criteria for the attention allocation task only: current or past ADHD diagnosis, Eye-tracking calibration difficulties (determined during study day). We would also like to add the Recruitme website as an advertising platform for the study.

Provide the rationale for the change(s)
We would like to add the exclusionary criteria for the attention allocation computer task only as the described criteria (ADHD diagnosis, and calibration difficulties), as these conflict with task administration. Specifically, ADHD diagnosis could be a confounding variable for the results of the attention allocation task and calibration difficulties would disable the task from being administered as the task cannot be operated without calibrating the eye-tracking machine to each specific patient. We would like to add Recruitme as an additional recruitment source in order to reach a larger population of potential subjects for this study.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
The proposed changes do not alter or affect risks or benefits to subjects.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
The proposed changes do not require a modification to the consent form.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

- ✓ Psychiatric Assessment
- ✓ Collection of Biological Specimens
- ✓ Medication Trial
- ✓ Psychotherapy Trial
- ✓ MRI
- ✓ Audio or Videotaping

Population

Indicate which of the following populations will be included in this research
✓ Adults

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
Gift Money through the RFMH business office.
Is the project externally funded or is external funding planned?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Approximately half of the individuals with posttraumatic stress disorder (PTSD) present with major depressive disorder (MDD). Compared to PTSD alone, patients with comorbid PTSD-MDD demonstrate greater distress and poorer treatment outcome. Functional magnetic resonance imaging (fMRI) show that relative to PTSD alone, PTSD-MDD is associated with decreased resting state functional connectivity (rs-FC) in both fear- and reward-processing circuits. In addition, our data suggest that Prolonged Exposure (PE), first-line PTSD treatment, may successfully target impairments in the fear circuits, but not in the reward circuits, which may explain the treatment-refractory quality of PTSD-MDD.
The goal of this pilot study is to collect preliminary data for future NIMH application, by testing the feasibility, safety and initial efficacy of an integrated therapeutic approach targeting both fear and reward impairments in PTSD-MDD patients. Specifically, we will examine a combination treatment with PE, shown to effectively address fear circuitry deficits, and Pramipexole, a dopamine agonist, shown to increase reward circuit function and to have promise in treating depression but not previously studied in PTSD. The central hypothesis is that combined PE/Pramipexole will a) improve PTSD and depressive symptoms in PTSD-MDD patients, and b) increase functional connectivity of fear and reward pathways as measured by fMRI rs-FC. In this pilot study, 15 adults aged 18-60 years with PTSD-MDD will receive combined 10-week of PE and Pramipexole up to the maximum dose of 4mg a day. They will clinically assessed at baseline, week 5, post treatment and at 3-month follow up, behaviorally assed on a probabilistic reward task (PRT) and attention allocation tasks, and fMRI scanned for resting state functional connectivity (rs-FC), at

baseline, and posttreatment.

Background, Significance and Rationale

Background, Significance and Rationale

Comorbid PTSD-MDD is common and is associated with greater severity and worse outcome than PTSD alone. Up to 50% of the PTSD cases, across multiple samples, have been shown to meet criteria for MDD (1, 2). Compared to PTSD alone, patients with PTSD-MDD exhibit greater distress (3), higher risk of suicide (4, 5), poorer treatment outcome (6), and impaired neurocognitive functioning (14). Despite these findings, no study to date has developed and examined novel treatments for patients with PTSD-MDD. There is a need for novel treatments for patients with PTSD-MDD. While cognitive behavioral therapy (CBT) approaches for PTSD have been generally shown to be effective, many patients do not benefit from these treatments. For PE, the gold standard CBT treatment for PTSD, non-response rates range from 25 to 60%, with dropout rates reaching 50% (15, 16). Few medications have been found to ameliorate PTSD, with only small effect sizes (17). One factor that was previously linked to treatment outcome in PTSD is emotional engagement (18, 19). However, since depression is frequently associated with emotion dysregulation, amotivation, and flattening of affect, it has been suggested that comorbid depressive symptoms in patients with PTSD may decrease emotional engagement, consequently hindering treatment efficacy (20). In sum, patients with PTSD-MDD may have poorer response to current treatments due to reduced emotional engagement and numbing symptoms.
SSRIs treatment has shown limited efficacy in PTSD. Previous reviews and meta-analyses of pharmacological treatments for PTSD have been mixed. Some reviews rated SSRIs as equivalent to trauma-focused psychological treatments (35, 36), including a Cochrane review (37). Several major reports, however, concluded poor efficacy of medication treatment for PTSD (38, 39, 40, 17). These findings suggest that a better understanding of the neurobiological processes underlying motivational symptoms and reward processing deficits in PTSD-MDD can potentially improve treatment development and ultimately personalized medicine.

PE alone may not target reward processing deficits in PTSD-MDD. The empirical evidence of decreased efficacy of PE in PTSD-MDD cited above is consistent with PE's hypothesized mechanism involving extinction processes (8, 41, 42) and not reward processing deficits.
Combining Pramipexole with PE may address limitations of PE alone by targeting reward processing and improving depressive symptoms. Agents enhancing dopamine neurotransmission with documented efficacy for depression (11, 43, 44) may be particularly useful for PTSD patients with comorbid MDD. Pramipexole is a dopamine agonist (D3) with strong evidence for anti-depressant efficacy (9, 10, 45-49) but that is yet to be studied in PTSD. There is a compelling theoretical rationale supporting the therapeutic utility of a dopamine agonist in this patient population, as PTSD-MDD is associated with anhedonia (30) and reward processing deficits (7). A wide array of findings, including studies of reward processing (50, 51), suggest that reward and motivation deficits are related to decreased dopaminergic function in reward circuitry. Relative to placebo, pramipexole treatment was associated with changes in a variety of reward-related brain regions. These pramipexole-induced effects on regional metabolism suggest a mechanism of antidepressant action that is distinct from that previously reported for serotonin reuptake inhibitor treatment and support a range of evidence that the central dopaminergic system plays a role in the pathophysiology of depression

(53-55).
Pramipexole was originally noted to improve mood in Parkinson's disease -- a meta-analysis of 14 RCTs of pramipexole for Parkinson's found that mood symptoms improved in 65% on pramipexole vs. 43% on placebo, and motivational symptoms improved 63% on pramipexole vs. 45% on placebo (56). Importantly, 10 studies (including controlled and open trials, and retrospective studies) of pramipexole support its efficacy for depression in patients without Parkinson's disease. A pooled analysis of three RCTs of pramipexole in psychiatric populations reported large effect sizes (0.6 - 1.1) in treating depression, based on the Hamilton Rating Scale for Depression (HRSD) (47). Tolerability of pramipexole in depressed patients has been comparable to that of approved antidepressant medications, with discontinuation rate of 9% based on pooled data from 253 patients in 8 studies. In our preliminary data in an open trial in MDD, pramipexole was highly efficacious and well-tolerated. Taken together, pramipexole has never been studied in PTSD, but it has shown promise in improving reward processing, altering reward network, and treating depression, providing a strong foundation for our plan to develop novel treatment for patients with PTSD-MDD.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
We hypothesize that combined treatment with PE/Pramipexole will improve PTSD and depressive symptoms and increase functional connectivity of fear and reward pathways as measured by fMRI.

Description of Subject Population

Sample #1

Specify subject population
PTSD-MDD
Number of completers required to accomplish study aims
15
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown

45% White
30% Black
15% Hispanic
10% Asian/Hawaiian/Pacific Islander

60% Females
40% Males

Description of subject population
All participants will have a diagnosis of PTSD-MDD based on SCID-V, CAPS-5 ≥ 25, and 17-item HRSD ≥ 17.

Recruitment Procedures

Describe settings where recruitment will occur
Anxiety Disorders Clinic
How and by whom will subjects be approached and/or recruited?

Patients will respond to an advertisement (see below "study advertised/ publicized") or be contacted by an RA after receiving a signed Permission to Contact form. Patient will call the clinic and after verbal is obtained consent the research assistant (RA) will conduct a preliminary phone screen that is part of a preexisting screening protocol (IRB #7094R). If the patient will be eligible for the study the RA will invite the patient for further screening at the clinic.

How will the study be advertised/publicized?
Patients will be informed of the study through: (a) word-of-mouth referrals from former patients, (b) referral from area medical and mental health professionals, (c) publicity about the study, including articles in local newspapers and magazines, our IRB approved website (http://columbiapsychiatry.org/trauma), **Recruitme Website**, IRB approved flyers, appearances on local radio and television shows, etc., leading to self-referral of prospective patients, (d) advertisements placed in local media and on the Internet
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
03765138

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Participants who are assessed for the following NYSPI IRB approved studies # 7136, #7489, #7469, and # 7464 will be offered to participate in the current study.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
PTSD-MDD
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria:	Method of Ascertainment:
1.Males or Females by the age of 18 and 60	History
2. Current DSM-V diagnosis of PTSD comorbid with MDD	SCID-V
3. CAPS-5 ≥ 25, and 17-item HRSD ≥ 17	CAPS-V, PCL-5, HRSD-17
4. Able to give consent, fluent in English	Clinical Interview
5. Not currently taking psychotropic medication	Clinical Interview and history

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criterion:	Method of Ascertainment:
1. Prior or current diagnosis with traumatic brain injury, bipolar disorder, psychotic disorder, gambling or impulse control disorders, or dementia	SCID-V and clinical interview
2. History of psychosis, psychotic disorder, mania or bipolar disorder	SCID-V and clinical interview
3. Severe substance use disorder excluding nicotine (i.e., nicotine use disorder and mild-moderate alcohol/cannabis use disorder are accepted)	SCID-V and clinical interview
4. Individuals at risk for suicide based on history and current mental state. BDI-II suicide item > 2 or CGI-Severity baseline score of 7.	HRSD-17, CGI, clinical interview
5. Treatment with antidepressants or other psychotropic medication in the past 4 weeks (or 6 weeks for fluoxetine; an exception will be made for zolpidem used intermittently for sleep).	Clinical interview and history
6. Pregnancy or plans to become pregnant during the period of the study.	Urine β-HCG, clinical interview
7. Current psychotherapy	Clinical interview
8. Current unstable or untreated medical illness	Clinical interview,

	physical exam, blood chemistry
9. Any condition that would exclude clinical MRI exam (e.g. pacemaker, paramagnetic metallic prosthesis, surgical clips, shrapnel, necessity for constant medicinal patch, some tattoos, severe obesity, claustrophobia)	Clinical interview, physical exam, MRI screening questionnaire
10. History of untoward reaction to pramipexole	Clinical interview, history
11. Prior or current diagnosis of OCD, Panic Disorder or Social Phobia	SCID-V and Clinical Interview
12. Medical diagnosis of Parkinson's disease	Clinical Interview, physical exam, blood chemistry
13. Eye tracking calibration difficulties as determined on day of study (Attention Allocation Task participants only)	**Calibration procedures**
14. Current or past ADHD diagnosis (Attention Allocation Task participants only)	**SCID-V and Clinical Interview**

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
7094R
Describe Study Consent Procedures

Research assistant will obtain verbal consent from patient in order to conduct a preliminary phonescreen. Phonescreening will be conducted as part of the Anxiety Disorders Clinic's preexisting screening protocol (IRB #7094R). If the patient will be eligible for the study the RA will invite him for further screening at the clinic.

At the clinic, patient will meet face to face with a person that is authorized to discuss and document consent (see "person designed to discuss and document consent"). After patient reads the consent the clinician will go over the consent with the patient and answer all the patient's questions. After answering all the patient's questions by the clinician patient will sign the study consent. The highest educational degree needed for the consenting clinician is a Doctor of Medicine degree (M.D.). Throughout this process, the patient will be told that they are free to refuse to participate in the research and that participation or non participation in research has no effect on their ability to continue to receive clinical care or services.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Campeas, Raphael, MD
Markowitz, John, MD
Sanchez-Lacay, jose, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study
The study consists of the following procedures: 1) screening and diagnostic assessments including: psychiatric interview and medical history, SCID interview, labs and urine drug screen, informed screening consent (3 hrs.); 2) informed study consent, baseline fMRI, behavioral task (2 hours); 3) Ten treatment visits and self-report forms, including CGI (1.5 hours); 4) Midpoint clinical assessment after treatment visit 5 and self-report forms (1 hour) ; 5) Follow up clinical assessment, follow up fMRI and behavioral task (2.5 hours); and 6) 3 month follow up clinical assessment and self-report forms.

4.A1. Preliminary Screening: Potential subjects will be screened by telephone by a research assistant after obtaining oral consent as a part of the Anxiety Disorders Clinic's preexisting screening protocol (IRB #7094R). Patients on prohibited psychoactive medication will be excluded and will not be tapered off such

medication for the purpose of entering this study. Psychiatric Diagnostic Evaluation: Patients deemed study eligible following preliminary screening will sign the Anxiety Disorders Clinic informed written consent for the psychiatric screening evaluation (IRB # 7094R). An experienced psychiatrist will evaluate presenting symptoms, psychiatric history, treatment history, medical history, trauma history, social and family history, and current medical status. Additional screening measures include: 1) collection of blood samples (20 cc) for chemistry profile, thyroid function tests, and CBC; 2) a urine sample for urinalysis and toxicology (and pregnancy for females); 3) structured interview (the SCID), CAPS-V, HRSD-17, CGI, CVC Suicide Risk Assessment and Screener and TBI performed by trained research team member; 4) a physical exam; 5) self-report forms: PCL-5, LEC-5, BDI-II and SHAPS
After obtaining informed consent and determining eligibility based on the above screening and laboratory testing, study visits will be scheduled.

4.A.2. fMRI Scan: Patients will undergo two fMRI sessions. MRI scans will be performed in the NYSPI 3.0T GE scanner and the 3T Siemens Prisma scanner at Zuckerman Institute MR Center. The scanning session will last approximately 30 minutes, with an additional 30 minutes total for set-up. Thus, the fMRI session lasts about 1 hour. Female subjects will have a urine pregnancy test on the day of the MRI scan, before being scanned. Structural MRI scan will be performed to quantify regional brain volumes and cortical thickness as well as provide a clinical reading by a neuroradiologist to forward results from the scan to the participant. Resting state fMRI will measure functional connectivity.

MRI Results
The results of the structural MRI will be shared with the subject and/or a physician of their choice, as detailed below. Because the structural MRI scan is being performed for research purposes only it may not show problems that would normally be found in a typical clinical MRI scan ordered by a doctor for a specific medical problem. The MRI scans obtained in this study may provide information that is clinically relevant. The quality of clinical information available from these images can vary widely, based on resolution, degree of motion artifact, and numerous aspects of the pulse sequences used to acquire them. All scans will be read by a clinical neuroradiologist (see “Personnel and Responsibilities”). As with any imaging procedure, if the radiologist determines that the quality of the scan does not lend itself to a clinical reading, he or she will provide written documentation to this effect. Only the radiologist may make this determination. The MRI will receive a clinical reading by a neuroradiologist within 4 weeks of the scan, and a confirmatory report will be written within 6 weeks of the scan as the following details. When the readings yield findings that are of urgent clinical concern, the radiologist (see “Personnel and Responsibilities”) will immediately provide an oral report followed by a handwritten or typed note to the PI, Yuval Neria, PhD, and the Director of the MRI Center. A final written transcript of the clinical reading will be provided within two weeks of the oral report. The radiologist will provide routine written reports to Dr. Neria within one month of image acquisition. Because T1 images are acquired in this study, all subjects will receive feedback about their scans in accordance with IRB policy. All results will be shared with research subjects in a manner that is consistent with the acuity and certainty of the finding, and will be communicated by an appropriately qualified member of the research team in the form of a letter that is approved by the IRB and will also be contacted by telephone if there is evidence of a clinically-significant abnormality. Results will be shared with the subject and/or a physician designated by the subject.

Probabilistic Reward Task (PRT): Subjects sit at a PC monitor and they are instructed to press a button to indicate whether a short (11.5 mm) or a long (13 mm) mouth was presented on a previously mouthless

cartoon face. The task includes three blocks of 100 trials. The difference between mouth sizes presented as well as the duration of stimulus exposure (100ms) is small, providing a setting in which a response bias may develop in response to asymmetric reinforcement: either the short or long mouth is rewarded ("Correct!! You won 20 Cents") three times more frequently ("rich stimulus") than correct identification of the other mouth ("lean stimulus"). In each block, only 40 correct trials (30 rich, 10 lean) are rewarded, so each subject is exposed to the same reward ratio. Subjects are informed that the purpose of this task is to win as much money as possible. Moreover, they are instructed that not all correct response will receive a reward feedback but they will be unaware that one of the stimuli will be disproportionately rewarded. Performance will be analyzed with respect to response bias, discriminability, and reaction time (RT), following prior procedures. This task will take approximately 25 minutes.

Attention Allocation Task: In each trial subjects will be shown a stimuli matrix containing 16 images, 6 negative and 6 neutral, for 6 seconds. The task is comprised of two 30 trial blocks. Participants will be asked to view the different image matrices freely with no specific instructions while being recorded by an eye-tracking apparatus collecting eye-movement data. Eye-tracking recording does not pose any danger or harm for participants. The task will take approximately 20 minutes.

4.A.3. Treatment: Prolonged Exposure (PE) Therapy. PE is a cognitive behavioral treatment, considered a "gold standard" treatment for PTSD, regardless of whether patients have comorbid depression or not. It will consist of 10 sessions of 90-minute duration, normally conducted once a week (note—make up for missed sessions are allowed within 10-12 week time frame). Therapists will follow the PE manual developed by Foa and colleagues and used in the Anxiety Disorders Clinic for more than a decade. Elements of PE include imaginal and in vivo exposure to trauma reminders; breathing retraining; cognitive restructuring; and PTSD psychoeducation. In each session, the patient recounts a trauma narrative, which is recorded on audiotape or electronically for daily home listening. The therapist helps the patient cognitively restructure his/her experience of the traumatic event. Each week the narrative is elaborated, becoming more detailed and exhaustive, until the patient habituates to it, extinguishing the anxiety it aroused. Each session the patient will also complete a BDI-II to track progress. Patients will see the same clinician for each of their treatment visits.

Pramipexole. In addition to receiving PE as described above, patients will have Pramipexole treatment administered by our team's psychiatrists who have expertise in PTSD pharmacotherapy and clinical trials. Initial dosing will follow the methods of Schneier (Preliminary Studies 3.3.B.6) and Goldberg (13): Daily dose will be started at 0.25 mg/day and increased by 0.25 mg/day every 3-4 days to a target of 2.5mg day by week 5. Beginning week 6 daily dose will be increased weekly by 0.5 mg/day to a maximum dose of 4mg. Adverse events will be systemically queried at each visit and vital signs will be checked. Compliance will be assessed by weekly pill count. Dose will be increased as tolerated unless the patient has achieved remission and will be decreased in the event of intolerable adverse events. Patients will check in with their treating psychiatrist for 15 minutes after every PE treatment session, for a total of 10 visits, normally conducted once a week (note—make up for missed sessions are allowed within 10-12 week time frame).Patients will see the same psychiatrist for each of their treatment visits. Staff psychiatrists carry beepers or cell phones and are available 24 hours per day for clinical emergencies. Patients will receive written information on how to contact staff by telephone or pager in the event of an emergency.

4.A.4. Midpoint Assessment (week 5): Patients will meet with a clinician and complete CAPS-V, HRSD-17,

CGI, CVC Suicide Risk Assessment and Screener and TBI performed by trained research team member and self-report forms: PCL-5, BDI-II and SHAPS.

4.A.5. Follow up visit: Patients will repeat fMRI scanning session and behavioral tasks. Procedures are identical to the first fMRI session. Follow up medical examinations, including physical exam, blood work, urinalysis will not be done routinely, but will be performed at any time during the study if clinically indicated by occurrence of a specific
adverse effect. In addition, patients will complete a follow up assessment with a CAPS-V, HRSD-17, CVC Suicide Risk Assessment and Screener and CGI performed by trained research team member; and self-report forms: PCL-5, BDI-II and SHAPS.

4.A.6. 3 Month follow up visit: Patients will meet with a clinician and complete CAPS-V, HRSD-17, CGI and TBI performed by trained research team member and self-report forms: PCL-5, BDI-II and SHAPS.
You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
At least weekly, the PI and study psychiatrist will review participants awaiting study procedures and will withdraw a person from the study if the participant:
1. Requests to be withdrawn from the study.
2. Reports significant suicidal ideation, as assessed by the clinician and/or by the BDI-II suicide item > 2
3. Symptomatic worsening, as measured by a score of 6 (much worse) or 7 (very much worse) on the CGl at any visit, or as per the treating psychiatrist's judgment
4. Is non-compliant with protocol requirements.
5. Manifests a new or inter-current illness that prevents the patient from complying with the protocol

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
20 cc of blood will be drawn for chemistry, CBC, and thyroid function tests.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Structured Clinical Interview for DSM-V (SCID) (60 minutes at screening)
Clinician Administered PTSD Scale (CAPS-5) (30 Minutes)
Hamilton Rating Scale for Depression (HRSD-17) (10 minutes)
Posttraumatic Stress Disorder Checklist (PCL-5) (5 minutes)
Structured Pill Count Interview (5 minutes)

Treatment Emergent Side Effect Scale (10 minutes)
Life Events Checklist (LEC) (5 minutes)
Clinical Global Impression Severity and Improvement (CGI) (5 minutes)
Snaith-Hamilton Pleasure Scale (SHAPS) (5 minutes)
Traumatic Brain Injury Identification Method (TBI) (5 minutes)
CVC Suicide Risk Assessment and Screener (10 minutes)
Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Pramipexole
Manufacturer and other information
Generic brands will be used and therefore will be made by multiple companies.
Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
The maximum delay to study treatment is two weeks. As a safety measure, weekly clinical check-ins by phone or in-person will occur. The patient will have immediate access to the psychiatrist who did the psychiatric intake evaluation, if he or she presents with an emergent clinical issue.
Maximum duration of delay to standard care or treatment of known efficacy
Prolonged Exposure (PE) is an active, first line treatment of PTSD (with or without concurrent MDD), with established efficacy. The maximum delay to PE is two weeks.
Treatment to be provided at the end of the study
Participants will be referred for further treatment as needed.

Clinical Treatment Alternatives

Clinical treatment alternatives
Other treatments used to treat PTSD and depression are SSRIs, such as paroxetine (Paxil) and setraline (Zoloft), which are the only medications approved, separately, for both PTSD and depression, as well as other psychotherapies include cognitive-behavioral therapy and approved medications, are available to participants outside of this research study and patients can discuss with their healthcare provider.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
MRI Scan: MRI scanning is not associated with any known medical risks, except for persons who have a heart pacemaker or have metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be screened by interview and questionnaire to determine the presence or absence of metallic objects, and informed that they cannot participate in the study if their body contains any paramagnetic metal other than standard dental work. Some people have reported sensations during MRI scans with the 3T magnet, such as “tingling” or “twitching” (or, very rarely, a painful sensation), which are caused by changes in the magnetic field. The MRI scanner also produces a loud noise; earplugs will be provided to reduce this discomfort. Some subjects become anxious and feel claustrophobic in the MRI scanner. If this is the case, staff will be available for help and support and, if the subject requests, the scan will be stopped. Women of child-bearing age will be required to have a pregnancy blood test at the time of medical screening and a pregnancy urine test on the day of the MRI scan. For women of child-bearing age, it will also be asked and it will be documented that they responded negatively (or procedure will not occur) to questioning on the MRI day (before the procedure is initiated) whether it is possible they may have become pregnant in the prior two-week period.

Prolonged Exposure treatment: Time-limited psychotherapies carry limited iatrogenic risks.
Patients may become distressed by the discussion of sensitive or painful material or by the experience of strong emotions during treatment. Some patients may find psychotherapy embarrassing or anxiety provoking, whether or not the treatment presses them to confront reminders of past traumas. A risk of any treatment is that it may be ineffective and that patients may not improve. Every effort will be made to insure patients’ comfort during treatment, and patients will be withdrawn if needed. Non-improvement and/or worsening. There is the risk that some patients will not improve clinically or will experience worsening of their symptoms during treatment.

Pramipexole: The most common adverse events reported for pramipexole in prior trials for depression in patients without Parkinson’s disease are nausea, sedation, and headache (2). In studies of restless legs syndrome, the following side effects were present in >2% and more common than in the placebo group: Nausea, constipation, diarrhea, dry mouth, fatigue, influenza, headache and somnolence. In studies of early Parkinson’s Disease, in which dosage tend to be higher than that proposed in this study, the following additional side effects were present in >1% and more common than in the placebo group asthenia, edema, malaise, fever, anorexia, dysphagia, weight loss, dizziness, insomnia, hallucinations (positively related to age), confusion, amnesia, hyperesthesia, dystonia, akathisia, thinking abnormalities, decreased libido,

myoclonus, vision abnormalities, impotence. Compulsive gambling has been reported as an adverse effect of pramipexole in persons with Parkinson's disease, but this has been reported rarely in persons treated for restless legs syndrome, and it has not been reported in persons treated for depression. Sleep attacks have also been reported in persons taking dopamine agonists for Parkinson's disease, but have not been reported for persons with restless legs or depression.
Interviews/assessments: Some subjects may find the interviews and assessment to be anxiety provoking or upsetting. Subjects will be informed that they may choose not to answer specific questions, and may stop the interview at any time if they are feeling uncomfortable. Every effort will be made to insure patients' comfort.

Blood-drawing: Drawing blood for tests may cause bruising around the needle site that may last days. Some may experience brief pain or discomfort at the needle entry site. There is also a rare risk of infection at the needle entry site. Some participants may feel dizzy; and bloods will be drawn with the participant in a supine position if there is a history of vasovagal syncopy in reaction to blood drawing. Proper sterile techniques will minimize the rare risk of infection.

Audiotaping: Some patients may feel uncomfortable about the evaluation sessions being audiotaped. The purpose of the audiotaping will be explained, confidentiality will be respected, and tapes will be erased after the spot checks or following supervision. Informed consent for taping will be obtained.

Describe procedures for minimizing risks
Minimizing risks of pramipexole:
a) Pramipexole will be initiated conservatively following procedures of Schneier and Goldberg (3) prior studies of depressed patients that resulted in low levels of adverse events. Daily dose will be started at 0.25 mg/day and increased by 0.25 mg/day every 3-4 days to a target of 2.5mg day by week 5. Beginning week 6 daily dose will be increased weekly by 0.5 mg/day to a maximum dose of 4mg. Dosage will be lowered or medication stopped if needed for adverse reactions. Patients will be carefully monitored for signs of daytime drowsiness and warned not to drive while drowsy if this occurs. Adverse events will be inquired about systematically through use of a checklist of side effects previously associated with pramipexole treatment, and vital signs will be assessed at each treatment visit.
b) Patients will be educated about potential adverse interactions with other medications they may wish to take and advised to contact study physicians before starting new medications.
c) Careful monitoring of patients weekly during study treatment by experienced clinicians. Patients will see the same clinician for each of their treatment visits. Staff psychiatrists carry beepers or cell phones and are available 24 hours per day for clinical emergencies. Patients will receive written information on how to contact staff by telephone or pager in the event of an emergency. In the event of clinically significant suicidal ideation or a medical or psychiatric emergency in the clinic, patients will be escorted to the emergency room of New York Presbyterian Medical Center, which is adjacent to New York State Psychiatric Institute.
d) Patients will be instructed to contact study personnel during treatment in the event of worsening of symptoms or significant adverse events. Patients who experience clinically significant worsening (CGI change score > 5) will have study treatment discontinued and will be given appropriate clinical care until stabilized. All patients leaving study treatment will be offered 6 months of free open treatment, after which time they will be referred to appropriate clinical treatment.

e) Patients will be consented prior to the start of study treatment, and they will be informed that they may withdraw from study treatment at any time.
f) At the conclusion of study treatment patients discontinuing pramipexole will have it discontinued gradually under supervision.
g) At the termination of PE/pramipexole treatment, patients will be offered six months of open treatment, including the option to continue PE and/or pramipexole, or to receive other therapy or medication treatments, if clinically indicated.

MRI Scan: Subjects will be screened by interview and questionnaire to determine the presence or absence of metallic objects, and informed that they cannot participate in the study if their body contains any paramagnetic metal other than standard dental work. Earplugs will be provided to reduce discomfort. Staff will be available for help and support and, if the subject requests, the scan will be stopped. Women of child-bearing age will be required to have a pregnancy blood test at the time of medical screening and a pregnancy urine test on the day of the MRI scan. For women of child-bearing age, it will also be asked and it will be documented that they responded negatively (or procedure will not occur) to questioning on the MRI day (before the procedure is initiated) whether it is possible they may have become pregnant in the prior two-week period.

Prolonged Exposure treatment: Every effort will be made to insure patients' comfort during treatment, and patients will be withdrawn if needed.

Interviews/assessments: Subjects will be informed that they may choose not to answer specific questions, and may stop the interview at any time if they are feeling uncomfortable. Every effort will be made to insure patients' comfort.

All patients will be assessed using the Columbia Veterans Center Suicide Risk Assessment and Screener instrument at intake, midpoint, and termination. Patients will also be continuously assessed by treating clinicians and by means of the BDI-II.

In the case of clinical deterioration or evidence of suicide risk, the on-call psychiatrist will be involved and available to see the patient right away and supervise the patient's management in the event of a serious problem such as worsening of suicidal ideation. In the occurrence of active suicidal ideation, the participant will be removed from research and be treated as clinically indicated.

For those deemed to be at greater than minimal risk at any time, the following steps will be taken:
• Provision of contact information for emergency services (911, Anxiety Disorders Clinic pager, NYC Mobile Crisis Team)
• Scheduling with ADC MD as soon as possible
• Completion of Safety Plan, copy of which is kept by patient
• Discussion of removal of means, including firearms
• Increased frequency of visits
• Phone check ins between sessions and upon missed appointment

For those at high risk, the following will be considered based on clinical judgment:
• Referral to high risk treatment program, such as DBT

• Emergency room (voluntary)
• Emergency room (involuntary)

For those who present with elevated risk at termination, we will offer:
• Referral to alternate or high risk treatment programs, as indicated

Blood-drawing: Proper sterile techniques will minimize the rare risk of infection.

Audiotaping: The purpose of the audiotaping will be explained, confidentiality will be respected, and tapes will be erased after the spot checks or following supervision. Informed consent for taping will be obtained.

Other Procedures for Minimizing Risk:
1) Careful medical and psychiatric screening to identify patients for whom risk for potential adverse effects are elevated. Such patients will be excluded from the study. As an example, an actively suicidal patient would be excluded from study participation and appropriate clinical treatment provided.
2) Patients with any of the following will be removed from research and treated openly or as clinically indicated: a) the occurrence of assaultive or illegal behavior; b) the occurrence of active suicidal ideation at any point during the trial as assessed by clinical interview; c) behaviors while intoxicated that are a danger to him/herself or others.
3) Inclusion of psychoeducation about PTSD, the treatment process and memory triggers within the therapeutic framework.
4) Careful monitoring of patients during pretreatment and study participation by experienced clinicians. Patients will see the same clinicians for each of their treatment visits.
5) Ability to remove any patient from the study who evidences significant clinical deterioration during acute treatment. Provisions will be made for appropriate clinical care of such patients.
6) Patients failing to benefit from the study treatment will be exited from the study and provided with appropriate clinical care based on weekly review with termination criteria (see section 4A.7).
7) All data will be coded and stored in locked files to insure confidentiality.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All data collected will be kept confidential and used for research purposes only. Patient charts will be kept in locked file cabinets identified by number. Access to research records is restricted to research staff and Federal, State, and Institutional regulatory authorities. Electronic data will be protected by password access. No subject's identifying data will be published.

MRI: The results of the structural MRI will be shared with the subject and/or a physician of their choice, as detailed below. Because the structural MRI scan is being performed for research purposes only it may not show problems that would normally be found in a typical clinical MRI scan ordered by a doctor for a specific medical problem. The MRI scans obtained in this study may provide information that is clinically

relevant. The quality of clinical information available from these images can vary widely, based on resolution, degree of motion artifact, and numerous aspects of the pulse sequences used to acquire them. All scans will be read by a clinical neuroradiologist (see "Personnel and Responsibilities"). As with any imaging procedure, if the radiologist determines that the quality of the scan does not lend itself to a clinical reading, he or she will provide written documentation to this effect. Only the radiologist may make this determination.

The MRI will receive a clinical reading by a neuroradiologist within 4 weeks of the scan, and a confirmatory report will be written within 6 weeks of the scan as the following details. When the readings yield findings that are of urgent clinical concern, the radiologist (see "Personnel and Responsibilities") will immediately provide an oral report followed by a handwritten or typed note to the co-investigator, Franklin Schneier, MD, and the Director of the MRI Center. A final written transcript of the clinical reading will be provided within two weeks of the oral report. The radiologist will provide routine written reports to Dr. Yuval Neria, PhD, within one month of image acquisition. Because T1 images are acquired in this study, all subjects will receive feedback about their scans in accordance with IRB policy. All results will be shared with research subjects in a manner that is consistent with the acuity and certainty of the finding, and will be communicated by an appropriately qualified member of the research team in the form of a letter that is approved by the IRB and will also be contacted by telephone if there is evidence of a clinically-significant abnormality. Results will be shared with the subject and/or a physician designated by the subject.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
All participants will receive a complete psychiatric evaluation and medical evaluation, results of which will be communicated to the participant's and their physician, at the participant's request. PTSD and MDD symptoms may improve as a result of the PE and pramipexole treatment, but patients will receive no direct benefit from fMRI or other study procedures. A potential benefit to society of this research is that the knowledge gained may provide future benefits for individuals with PTSD-MDD in terms of improved understanding of brain function in PTSD-MDD, which may improve future treatments.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Study participants will receive $100.00 for the completing the first MRI visit ($16.20 for completion of the Probabilistic Reward Task, $20 for completion of the self-report tasks and $63.80 for completion of the MRI), $100 for completing the second MRI visit ($16.20 for the Probabilistic Reward Task $20 for completion of the self-report tasks and $63.80 for completion for the MRI). Participants will receive 30$

for completion of the midpoint evaluation (clinician assessment and self-report forms). Participants will also receive an additional $50 for completing the 3-month follow up (clinician assessment and self-report forms). Study patients will receive up to a total of $280 for their participation in the study. Compensation will be pro-rated if the subject does not complete all the study procedures. Payments to subjects will be in the form of a check payable by RFMH mailed to the participant within 4-6 weeks of the end of the subject's study participation.

References

References
1. Rytwinski NK, Avena JS, Echiverri-Cohen AM, Zoellner LA, Feeny NC. The relationships between posttraumatic stress disorder severity, depression severity and physical health. J Health Psychol. 2014;19:509-520.
2. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52:1048-1060.
3. Blanchard EB, Buckley TC, Hickling EJ, Taylor AE. Posttraumatic stress disorder and comorbid major depression: is the correlation an illusion? J Anxiety Disord. 1998;12:21-37.
4. Ramsawh HJ, Fullerton CS, Mash HB, Ng TH, Kessler RC, Stein MB, Ursano RJ. Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. J Affect Disord. 2014;161:116-122.
5. Oquendo MA, Friend JM, Halberstam B, Brodsky BS, Burke AK, Grunebaum MF, Malone KM, Mann JJ. Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. Am J Psychiatry. 2003;160:580-582.
6. Green BL, Krupnick JL, Chung J, Siddique J, Krause ED, Revicki D, Frank L, Miranda J. Impact of PTSD comorbidity on one-year outcomes in a depression trial. J Clin Psychol. 2006;62:815-835.
7. Zhu X, Helpman L, Papini S, Schneier F, Markowitz JC, Van Meter PE, Lindquist MA, Wager TD, Neria Y. Altered resting state functional connectivity of fear and reward circuitry in comorbid PTSD and major depression. Depress Anxiety. 2017;34:641-650.
8. Helpman L, Marin MF, Papini S, Zhu X, Sullivan GM, Schneier F, Neria M, Shvil E, Malaga Aragon MJ, Markowitz JC, Lindquist MA, Wager T, Milad M, Neria Y. Neural changes in extinction recall following prolonged exposure treatment for PTSD: A longitudinal fMRI study. Neuroimage Clin. 2016;12:715-723.
9. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety. 2000;11:58-65.
10. Cusin C, Iovieno N, Iosifescu DV, Nierenberg AA, Fava M, Rush AJ, Perlis RH. A randomized, double-blind, placebo-controlled trial of pramipexole augmentation in treatment-resistant major depressive disorder. J Clin Psychiatry. 2013;74:e636-641.
11. Fawcett J, Rush AJ, Vukelich J, Diaz SH, Dunklee L, Romo P, Yarns BC, Escalona R. Clinical Experience With High-Dosage Pramipexole in Patients With Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression. Am J Psychiatry. 2016;173:107-111.
12. Schneier FR, Slifstein M, Whitton AE, Pizzagalli DA, Reinen J, McGrath PJ, Iosifescu DV, Abi-Dargham A. Dopamine release in antidepressant-naïve major depressive disorder: a multimodal [11C]-(+)-PHNO positron emission tomography and functional magnetic resonance imaging study. Biological Psychiatry.
13. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of

pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry. 2004;161:564-566.
14. Nijdam MJ, Gersons BP, Olff M. The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder. Eur J Psychotraumatol. 2013;4.
15. Schottenbauer MA, Glass CR, Arnkoff DB, Tendick V, Gray SH. Nonresponse and Dropout Rates in Outcome Studies on PTSD: Review and Methodological Considerations. Psychiatry: Interpersonal and Biological Processes. 2008;71:134-168.
16. Bradley R, Greene J, Russ E, Dutra L, Westen D. A multidimensional meta-analysis of psychotherapy for PTSD. Am J Psychiatry. 2005;162:214-227.
17. Hoskins M, Pearce J, Bethell A, Dankova L, Barbui C, Tol WA, van Ommeren M, de Jong J, Seedat S, Chen H, Bisson JI. Pharmacotherapy for post-traumatic stress disorder: Systematic review and meta-analysis. British Journal of Psychiatry. 2018;206:93-100.
18. Jaycox LH, Foa EB, Morral AR. Influence of emotional engagement and habituation on exposure therapy for PTSD. Journal of Consulting and Clinical Psychology. 1998;66:185-192.
19. Rauch S, Foa E. Emotional Processing Theory (EPT) and Exposure Therapy for PTSD. Journal of Contemporary Psychotherapy. 2006;36:61-65.
20. Angelakis S, Nixon RDV. The Comorbidity of PTSD and MDD: Implications for Clinical Practice and Future Research. Behaviour Change. 2015;32:1-25.
21. Shvil E, Rusch HL, Sullivan GM, Neria Y. Neural, psychophysiological, and behavioral markers of fear processing in PTSD: a review of the literature. Curr Psychiatry Rep. 2013;15:358.
22. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. Biol Psychiatry. 2006;60:376-382.
23. Lissek S, Powers A, McClure E, Phelps E, Woldehawariat G, Grillon C, Pine D. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behaviour research and therapy. 2005;43:1391-1424.
24. Graham BM, Milad MR. The study of fear extinction: implications for anxiety disorders. Am J Psychiatry. 2011;168:1255-1265.
25. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66:1075-1082.
26. Kaczkurkin AN, Burton PC, Chazin SM, Manbeck AB, Espensen-Sturges T, Cooper SE, Sponheim SR, Lissek S. Neural Substrates of Overgeneralized Conditioned Fear in PTSD. American Journal of Psychiatry. 2016;174:125-134.
27. Buckley TC, Blanchard EB, Neill WT. Information processing and ptsd: A review of the empirical literature. Clinical Psychology Review. 2000;20:1041-1065.
28. Paunovic N, Lundh LG, Öst LG. Attentional and memory bias for emotional information in crime victims with acute posttraumatic stress disorder (PTSD). Journal of Anxiety Disorders. 2002;16:675-692.
29. Nawijn L, van Zuiden M, Frijling JL, Koch SBJ, Veltman DJ, Olff M. Reward functioning in PTSD: A systematic review exploring the mechanisms underlying anhedonia. Neuroscience & Biobehavioral Reviews. 2015;51:189-204.
30. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci. 2015;17:141-150.
31. Hopper JW, Pitman RK, Su Z, Heyman GM, Lasko NB, Macklin ML, Orr SP, Lukas SE, Elman I. Probing Reward Function in Posttraumatic Stress Disorder: Expectancy and Satisfaction with Monetary Gains and Losses. Journal of psychiatric research. 2008;42:802-807.
32. Sailer U, Robinson S, Fischmeister FPS, König D, Oppenauer C, Lueger-Schuster B, Moser E, Kryspin-

Exner I, Bauer H. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. Neuropsychologia. 2008;46:2836-2844.
33. Elman I, Lowen S, Frederick BB, Chi W, Becerra L, Pitman RK. Functional Neuroimaging of Reward Circuitry Responsivity to Monetary Gains and Losses in Posttraumatic Stress Disorder. Biological Psychiatry. 2009;66:1083-1090.
34. Sailer U, Robinson S, Fischmeister FP, Konig D, Oppenauer C, Lueger-Schuster B, Moser E, Kryspin-Exner I, Bauer H. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. Neuropsychologia. 2008;46:2836-2844.
35. Association AP: Practice Guidelines for the Treatment of Patients with Acutre Stress Disorder and Posttraumatic Stress Disorder. American Psychiatric Press; 2004.
36. Foa EB KT, Friedman MJ, Cohen J, eds: Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies, Guilford; 2008.
37. Stein DJ, Zungu-Dirwayi N, van der Linden GJH, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). The Cochrane Database of Systematic Reviews. 2000.
38. Health NCCfM. Post-traumatic Stress disorder: The Management of PTSD in Adults and Children in Primary and Secondary Care. British Psychological Society/Royal College of Psychiatrists. 2005.
39. Health ACfPM. Australian Guidelines for the Treatment of Adults with Acutre Stress Disorder and Posttraumatic Stress Disorder. ACPMH. 2007.
40. Institute of Medicine: Treatment of PTSD: An Assessment of the Evidence, National Academies Press; 2008.
41. Helpman L, Papini S, Chhetry BT, Shvil E, Rubin M, Sullivan GM, Markowitz JC, Mann JJ, Neria Y. Ptsd Remission after Prolonged Exposure Treatment Is Associated with Anterior Cingulate Cortex Thinning and Volume Reduction. Depress Anxiety. 2016;33:384-391.
42. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. Psychol Bull. 1986;99:20-35.
43. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Archives of General Psychiatry. 2007;64:327-337.
44. CB A. Pramipexole in psychiatry: a systematic review of the literature. Journal of Clinical Psychiatry. 2007;68:1230-1236.
45. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, Gemignani A, Battistini G, Bassi A, Abelli M, Cassano GB. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. Bipolar Disord. 2002;4:307-314.
46. Inoue T, Kitaichi Y, Masui T, Nakagawa S, Boku S, Tanaka T, Suzuki K, Nakato Y, Usui R, Koyama T. Pramipexole for stage 2 treatment-resistant major depression: an open study. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34:1446-1449.
47. Aiken CB. Pramipexole in psychiatry: a systematic review of the literature. J Clin Psychiatry. 2007;68:1230-1236.
48. Paolo C, Lorenzo L, Federico S, Serena N, Giulia B, Alfredo G, Battista CG. Pramipexole in treatment-resistant depression: An extended follow-up. Depression and Anxiety. 2004;20:131-138.
49. Franco-Chaves JA, Mateus CF, Luckenbaugh DA, Martinez PE, Mallinger AG, Zarate CA. Combining a dopamine agonist and selective serotonin reuptake inhibitor for the treatment of depression: A double-blind, randomized pilot study. Journal of affective disorders. 2013;149:319-325.
50. Bergamini G, Sigrist H, Ferger B, Singewald N, Seifritz E, Pryce CR. Depletion of nucleus accumbens dopamine leads to impaired reward and aversion processing in mice: Relevance to motivation pathologies. Neuropharmacology. 2016;109:306-319.

51. Frank S, Veit R, Sauer H, Enck P, Friederich H-C, Unholzer T, Bauer U-M, Linder K, Heni M, Fritsche A, Preissl H. Dopamine Depletion Reduces Food-Related Reward Activity Independent of BMI. Neuropsychopharmacology. 2016;41:1551-1559.
52. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of Increasing Monetary Reward Selectively Recruits Nucleus Accumbens. The Journal of Neuroscience. 2001;21:RC159-RC159.
53. Kapur S, John Mann J. Role of the dopaminergic system in depression. Biological Psychiatry. 1992;32:1-17.
54. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nature reviews Neuroscience. 2016;17:524-532.
55. Belujon P, Grace AA. Dopamine System Dysregulation in Major Depressive Disorders. International Journal of Neuropsychopharmacology. 2017;20:1036-1046.
56. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. Clin Ther. 2009;31:89-98.
57. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Statistical Methods in Medical Research. 2013;22:278-295.
58. Trials PoHMDiC: The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC, National Research Council; 2010.
59. Roderick JAL, Wang Y. Pattern-Mixture Models for Multivariate Incomplete Data with Covariates. Biometrics. 1996;52:98-111.

Uploads

Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
7692 Recruitme Ad.pdf
7692 Recruitme Ad2.pdf
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study

7692 Recruitme Ad

Approximately half of the individuals with Posttraumatic Stress Disorder (PTSD) present with major depressive disorder (MDD). Compared to PTSD alone, patients with comorbid PTSD-MDD demonstrate greater distress and poorer treatment outcome. Functional magnetic resonance imaging (fMRI) show that relative to PTSD alone, PTSD-MDD is associated with decreased resting state functional connectivity (rs-FC) in both fear-and reward-processing circuits. In addition, our data suggest that Prolonged Exposure (PE), first-line PTSD treatment, may successfully target impairments in the fear circuits, but less so in the reward circuits, which may explain the treatment-refractory quality of PTSD-MDD. The goal of this pilot study is to collect preliminary data on the feasibility, safety, and initial efficacy of an integrated therapeutic approach targeting both fear and reward impairments in PTSD-MDD patients. Specifically, we are examining a combination treatment with PE, shown to effectively address fear circuitry deficits, and Pramipexole, a dopamine agonist, shown to increase reward circuit function and to have promise in treating depression but not previously studied in PTSD. The central hypothesis is that combined PE/Pramipexole will a) improve PTSD and depressive symptoms in PTSD-MDD patients and b) increase functional connectivity of fear and reward pathways as measured by fMRI rs-FC.

Currently Recruiting Participants- Call Shay Arnon at 646-774-8106 for more information.

Recruitme Screening Questions:

1. Are you between the ages of 18 and 60?
2. Are you not currently on psychotropic medications (i.e. antidepressants)?
3. Have you ever experienced a traumatic event (such as a sexual or physical assault, natural disaster, combat)?
4. Do you experience nightmares or thinking about the traumatic event when you don't want to?
5. Do you feel constantly on guard, watchful, or easily startled?
6. Do you experience feeling guilty or down on yourself?
7. Do you experience feeling very restless or slowed down?

7692 Recruitme Ad

Approximately half of the individuals with Posttraumatic Stress Disorder (PTSD) present with major depressive disorder (MDD). Compared to PTSD alone, patients with comorbid PTSD-MDD demonstrate greater distress and poorer treatment outcome. The goal of this pilot study is to collect preliminary data on the feasibility, safety, and initial efficacy of an integrated therapeutic approach of a combination treatment with PE and Pramipexole, a dopamine agonist, in treating patients suffering with PTSD and Depression. This study includes pre and post treatment research MRI Scans.

Currently Recruiting Participants- Call Shay Arnon at 646-774-8106 for more information.

Recruitme Screening Questions:

1. Are you between the ages of 18 and 60?
2. Are you not currently on psychotropic medications (i.e. antidepressants)?
3. Have you ever experienced a traumatic event (such as a sexual or physical assault, natural disaster, combat)?
4. Do you experience nightmares or thinking about the traumatic event when you don't want to?
5. Do you feel constantly on guard, watchful, or easily startled?
6. Do you experience feeling guilty or down on yourself?
7. Do you experience feeling very restless or slowed down?