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Tianeptine for Treatment Resistant Depression

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability in adults worldwide (~16M patients in US alone). Unfortunately, only ~40% of patients achieve full remission following first-line treatment with a selective serotonin reuptake inhibitor (SSRI), creating a pressing need for new therapeutic approaches to address treatment-resistant depression. One strategy for improving treatment response recognizes the potential for underlying mechanistic heterogeneity in MDD and the associated need for focused treatments targeting biologically distinct subgroups of MDD patients. Significant evidence suggests dysfunction of endogenous opioid signaling pathways as a key biological deficit in some MDD patients. Before the advent of electroconvulsive therapy and tricyclic antidepressants in the 1950s, the administration of opioid receptor agonists was unsystematically used for treatment of depression. Several case studies and small clinical trials have pointed to the efficacy of opioid agonists in treating MDD, with some limited evidence in treatment-resistant patients as well. Relatedly, deficiencies in physical and emotional pain modulation observed in depressed patients are likely to be linked with underlying dysfunction in endogenous opioid signaling. Patients with MDD report physical pain symptoms more than twice as often as non-depressed individuals[1–3], chronic pain is a significant risk factor for developing depression[4], and the presence of comorbid pain is a negative prognostic factor for antidepressant treatment[5]. Functional magnetic resonance imaging (fMRI) studies suggest that physical pain and social rejection activate common brain regions, such as the dorsal anterior cingulate cortex (dACC) and anterior insula (aINS)[6,7]. Moreover, emotional pain resulting from adverse social experiences (e.g., childhood abuse and neglect, romantic rejections, etc.) increases vulnerability to depression[8,9], and reduced pleasure from social interactions contributes to withdrawal, reduced social support, and the persistence of a depressive episode once it develops[10].

We hypothesize that a subgroup of MDD patients with deficient opioid receptor signaling will better respond to pharmacological interventions specifically targeting this biological mechanism. Studies from our laboratories show that endogenous opioids act at the mu-opioid receptor (MOR) in response to social rejection and that this response is dramatically blunted in depressed individuals.[11] In addition, preliminary data from our lab show that healthy individuals with high trait rejection sensitivity (RS) also show reduced MOR activation, similar to depressed individuals. Notably, approximately one third of all patients with MDD have a "long-standing pattern of interpersonal rejection sensitivity"[12–14], a common feature in, although not restricted to, the "atypical" subtype of MDD[15–17]. Thus, high RS may represent the behavioral manifestation of

underlying deficits in endogenous opioid signaling and blunting of opioid release observed in some depressed patients in response to social rejection.[11] Indeed, our recent fMRI study showed that women with MDD display exaggerated emotional and neural responses to social rejection, particularly in the right anterior insula.[18] In response to social acceptance, women with MDD responded with positive emotions, however neural activity in the nucleus accumbens, a reward structure, was dissociated from subjective happiness.[18] Since MOR regulates social distress and social reward in animals[19–28] and humans[11,29], interventions targeting this mechanism may be *more effective than conventional treatments in treating high RS MDD* by regulating the neural pathways activated during social rejection and social acceptance.

In this application, we propose to target MOR signaling in depressed patients with tianeptine. Tianeptine is an atypical antidepressant that has been used clinically in Europe, Asia, and South America since the late 1980s in millions of patients.[30-34] Its efficacy in humans is well documented, and comparable to, or better, than that of several commonly used classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).[30-40] However, tianeptine's molecular mechanism of action had remained unknown until recently. Work in our laboratories has shown that tianeptine acts as a selective agonist of MOR, signaling in a manner analogous to enkephalins and endorphins, the endogenous opioid peptides.[41,42] Using both genetic knockout and pharmacological inhibition in mouse models for the study of depression, we have collected strong evidence that MOR is the direct molecular target by which tianeptine exerts its antidepressant effects, an entirely unique mechanism among existing antidepressants. Importantly, at clinical doses, tianeptine does not produce euphoria; in fact, at 6 times the normal dose, patients reported no euphoria.[43] Furthermore, unlike treatment of pain by traditional opioid agonists, prolonged occupancy of the receptor is not required for the antidepressant effect. Instead, much like the hypothesized pulsatile and time-limited action of endogenous opioids in response to social rejection and acceptance, tianeptine-induced MOR agonism sets in place a signaling cascade that leads to lasting physical changes in dendritic structure in key brain circuits.[44,45] Of note, tianeptine was never approved for clinical use in the US, but has been used safely and widely throughout Europe, Asia, and South America for decades.

The major goals of this project are (1) to define the relationship between opioid signaling deficits and response to tianeptine treatment, (2) to develop a comprehensive assessment battery capable of identifying endogenous opioid signaling deficits to explore biological heterogeneity in the MDD population, and (3) ultimately to improve the response rate compared to standard of care in a subgroup of MDD patients selected based on biomarkers of opioid signaling deficiencies.

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2. General Design

2.1. Study sites and organizational structure.

The studies proposed in this application will be conducted in parallel at two sites: the the Mood and Anxiety Disorders Program at the Icahn School of Medicine at Mount Sinai (MSSM), and Stanford Depression Research Clinic at Stanford University School of Medicine (SUSM). In addition, MRI studies for the MSSM patients will be carried out at the New York State Psychaitric Institute (NYSPI). The following procedures will be approved by the local Institutional Review Boards (IRBs) at each site, where the site PIs (Alla Landa, PhD, NYSPI, James Murrough, MD at MSSM, and Alan Schatzberg, MD at SUSM) will be responsible for overseeing conduct of the study at their respective site. As the lead institution, NYSPI will be responsible for managing the finances of the project and overseeing database management, and regulatory/reporting functions. Jonathan Javitch, MD, PhD at Columbia University and NYSPI is the overall study PI and maintains responsibility for study-wide decisions involving study logistics and the scientific direction of the project.

We have chosen to recruit subjects and perform all assessments except for neuroimaging procedures at the two sites (N=24 at each site for overall study N=75, 28 already entered), which will increase the rate of participant enrollment, ensure that recruitment goals are met, and enhance the generalizability of the sample. Structural and task-based magnetic resonance imaging (MRI) will be performed solely under Dr. Landa's direction at NYSPI in order to maintain internal validity of the data set. MSSM subjects will be transported to NYSPI to complete neuroimaging procedures as described below.

2.2. Subject recruitment and screening procedures.

Recruitment will proceed in parallel at each study site by means of (1) screening individuals who directly contact the clinical programs at MSSM and SUSM, (2) referral from clinicians in other disciplines at the component institutions participating in this project, and (3) outreach to the communities surrounding MSSM and SUSM. We also promote recruitment of under represented minority subjects by anticipating and working to eliminate barriers to research participation. Promotional materials at each component clinic allay these concerns by explaining how our studies are designed to mitigate and overcome these barriers to participation in research studies.

Potential subjects will be evaluated by remote and/or in-person meetings. Those who decide to participate by signing informed consent will have an evaluation inclusive of a clinical interview by a study clinician, structured diagnostic interview, and completion of standardized rating scales (trained rater) in order to document eligibility. Eligible subjects will have further documentation of vital signs, medical history urine drug screen, CBC, chemistries and electrolytes, thyroid profile, urine analysis, standing/supine systolic/diastolic BP, and ECG. Female participants will undergo urine pregnancy testing to confirm that they are not pregnant prior to drug initiation and will be instructed to use effective birth control during the study, such as condoms, IUDs, oral contraceptives, or depot contraceptives. Participants also will be scheduled for further baseline testing as described below.

2.3. Imaging procedures.

Pre- and post-treatment brain MRI for subjects enrolled at MSSM will be performed on each subject using a 3T Siemens Prisma scanner located at NYSPI. Participants from the MSSM site will have transportation arranged and paid at the study's expense. Subjects will be compensated for their time spent in transit in addition to regular compensation for MRI procedures.

At the start of the scanning session, a 3-Plane localizer (scout) will be acquired to determine patient position. Subjects will then receive (1) T1-weighted 3D for volumetric analysis and coregistration of functional MRI data, (2) EPI scan during Thermal pain sensitivity task, (3) EPI scan during Social Feedback task, and (4) EPI scan while Resting. For the MRI procedures, participants are instructed to lie as still as possible within the magnet. The MRI scan is completed in one session lasting for a total of 60 minutes. All precautions and protections are given to the participant to ensure that they are as safe and as comfortable as possible. The participant is given a squeeze ball to terminate the scan at any time. Conducting these procedures will be an accredited Magnetic Resonance Technologist and one member of the research staff (Bachelor's Level or Higher).

MRI data will be analyzed with Statistical Parametric Mapping (SPM). We will conduct a whole-brain analysis in a voxel-by-voxel brain-wide search as well as hypothesis-driven region of interest (ROI) analysis (Bonferroni-corrected alphas for multiple VOIs) to examine brain areas (e.g., amygdala, nucleus accumbens, ventrolateral prefrontal cortex, anterior cingulate cortex, anterior insula) previously shown to regulate responses to physical pain as well as positive and negative social stimuli. Statistical parametric maps are obtained using whole-brain image subtraction routines with the images warped to standardized space.

Thermal Pain Sensitivity Task: Thermal stimulations will be delivered to left volar forearm using an MRI-safe delivery system. Series of 10 second stimuli will be administered, each followed by an 18-22 seconds rest period. We will administer series of moderately painful temperatures (one subjectively rated as level 6 on a 0-10 VAS scale and one standard temperature of 45^{o}) in a semi-random order (random for participant, same order across subjects). With a calibration procedure performed before the MRI,[1] we will choose the temperature to administer in fMRI on a participant-by-participant basis to be sure that the subjective pain intensity is constant across participants. During the task itself, participants are asked to stare at a fixation cross during each trial and focus on the sensations elicited by the somatic stimulus. Participants are then instructed how to rate their after each trial trial using ten-point VAS scales . In the

second part of pain task, instead of resting between pain stimuli participants are asked to interact with other by playing a computer ball-tossing game.

Social feedback task: Prior to the scanning session, all subjects will complete an "online profile" (e.g., gender, age, birthdate, race/ethnicity, orientation, major/occupation, hobbies, personal qualities, years of education, etc.) and provide a digital photo of her/himself prior to rating profiles of others. If subjects do not have a photo available or prefer, they may have a digital photo taken during the interview. All subjects then complete online ratings of personal profiles from a collection of over 500 men and women with whom they would be most interested in forming a close personal relationship. Subjects will be informed that this task is a simulation, and that others' ratings of the subject are not "real." During the scanning session, subjects are presented with their own picture along with a picture of a highly rated profile, along with feedback that they were liked (acceptance trial), not liked (rejection trial), or that others were undecided or had not yet rated them (neutral trial). Questionnaires will be given before, during, and/or after the task to assess cognitive and emotional states. For questionnaires, answer choices are presented on Likert scale (e.g., 5 discrete choices), or a visual analogue scale (e.g., a sliding scale), verbally, on paper, or on a computer.

2.4. Comprehensive assessment of physical and emotional pain functioning.

The hypothesis under investigation in this study is that a subgroup of depressed outpatients experience brain opioid signaling dysfunction, which manifests behaviorally as increased physical and emotional pain sensitivity, and will be predictive of greater response to tianeptine (i.e., due to its mu-opioid receptor agonism). In addition to the imaging procedures described above, this hypothesis will be further studied by having participants complete a assessment battery testing pain functioning at baseline and study endpoint, in addition to further weekly assessments of selected measures.

All subjects will complete the baseline evaluation, which includes psychiatric assessments (HARS, STAI, IDS-SR, CGI, MMSE), physical pain tests (Thermal Sensitivity Test, BPI, Physical and Psychological Pain Scale), as well as emotional pain and interpersonal wellbeing tests (ARSQ, C-SSRS, Psychache scale, Perceived Stress Reactivity Scale (PSRS), Perceived Stress Scale, Shyness and Sociability Scale, Reaction to Implied Rejection Measure, Hurt Feelings Questionnaire, Multidimensional Scale of Perceived Social Support)

2.5. Summary of visit schedule and other study assessments.

As described above, at Screening, patients who decide to participate by signing informed consent will undergo a psychiatric clinical interview, and eligibility is determined by assessments with the Structured Clinical Interview Diagnostic for DSM 5 (SCID) and 24-item Hamilton Rating Scale for Depression (HRSD). Eligible subjects will complete screening laboratory tests and those currently taking other antidepressant medications will be tapered off under the supervision of the research staff according to standard clinical practice or by the doctor currently prescribing the medication. There will be a 5 day wash-out period from the time the previous antidepressant has been stopped before tianeptine is started, 3 weeks if the previous antidepressant was a monoamine oxidase inhibitor and 4 weeks if the antidepressant was fluoxetine. For participants requiring an antidepressant taper, the screening psychiatric assessments will be repeated post-

taper to confirm inclusion criteria are still met. Eligible subjects will then complete the remainder of the baseline evaluation, which includes the Hamilton Anxiety Rating Scale (HARS), State Trait Anxiety Inventory (STAI), Inventory of Depressive Symptomatology—Self Report (IDS-SR), Clinical Global Impressions (CGI) Severity and Improvement, Mini Mental State Examination (MMSE), physical pain tests (BPI), emotional pain tests (ARSQ, C-SSRS, Psychache scale), Drug Abuse Screen Test (DAST), and Michigan Alcohol Screen Test (MAST). Finally, for patients who are willing to participate, whole-blood samples will be drawn and used to screen for genetic polymorphisms in the genes for the mu-opioid receptor (e.g., A118→G), oxytocin receptor, vasopressin receptor 1A, and monoamine oxidase A, all of which have been shown to moderate behavioral and neural responses to rejection. Blood samples will be stored for future analysis if other potential genetic biomarkers are later identified.

Following screening and baseline measures, subjects will undergo MRI scanning, which is performed prior to Week 0. At Week 0, tianeptine medication will be initiated at 12.5 mg po tid. The first dose of tianeptine 12.5 mg is given at the Week 0 appointment under the supervision of study staff so that initial response can be observed. Subjects will be instructed not to consume any food for at least 3 hours prior to their appointment to control any food effect on tianeptine's pharmacokinetics. Orthostatic blood preasure and heart rate will be measured before tianeptine administration, subjects will be observed for a period of 1 hour.

Subjects return at Weeks 1, 2, 3, 4, 5, 6, 7, and 8 (+/– 2 days) for depression follow-up visits and complete the HRSD, CGI Severity and Improvement, IDS-SR, and Structured Pill Count Interview. At baseline, week 4 and week 8 subjects will also repeat the following tests: HARS, VAS Physical and Psychological Pain Scale. Perceived Stress Reactivity Scale (PSRS), Perceived Stress Scale Psychache Scale, UCLA Loneliness Scale, Shyness and Sociability. Reaction to Implied Rejection Measure. Hurt Feelings Questionnaire. Adult Rejection Sensitivity Questionnaire, Multidimensional Scale of Perceived Social Support, Brief Pain Inventory (BPI).. All baseline measures will be repeated at study endpoint (Week 8), including a post-treatment MRI scanning visit at NYSPI.

Revised table of procedures and timetable is shown below:

Procedures and Assessments	Timepoints									
	Screening	Baseline w0	w1	w2	w3	w4	w5	w6	w7	End of Tx w8
Informed Consent	x									
Inclusion/Exclusion	x									
Vital Signs[a]	x	x				x				x
ECG	x	x*								x
Clinical Labs[b]	x					x				x
Liver Function Test	x					x				x
Blood Genomics	x**					x**				x**
Urine Pregnancy Test[c]	x	x								x
Urinalysis	x									
Drug Screening	x									
MRI Eligibility Screener	x	x								x
Facial Recognition Task (csv)		x								x
Thermal Calibration (csv)		x								x
Imagery Training, fMRI instructions, practice		x								x
Localizer/Structural MRI/Field Map		x								x
Social Feedback Task (csv)		x								x
Resting State		x								x
Thermal Pain Task (csv)		x								x
Visual Analogue Scale-Body Pain		x								x
Social Feedback Follow-Up		x								x
Study Medication Dispensation		x		x		x		x		x
Demographics/Profile Ratings	x	x								
Taper Antidepressant Medication[d]	x									
ATHF	x									
Medical History	x									
SCID	x									
MMSE	x									
Clinical/Medication Progress Note	x	x	x	x	x	x	x	x	x	x
Pill Count			x	x	x	x	x	x	x	x
AE Assessment		x	x	x	x	x	x	x	x	x
HRSD 24-item	x	x	x	x	x	x	x	x	x	x
HARS		x				x				x
CGI S/I	x	x	x	x	x	x	x	x	x	x
CSSR-S		x								x
Social Feedback Profiles rating		x								x
IDS-SR		x	x	x	x	x	x	x	x	x
VAS Physical and Psychological Pain Scale		x		x		x		x		x
Perceived Stress Reactivity Scale (PSRS)		x				x				x
Perceived Stress Scale		x				x				x
Psychache Scale		x				x				x
UCLA Loneliness Scale		x				x				x
Shyness and Sociability		x				x				x
Reaction to Implied Rejection Measure		x				x				x
Hurt Feelings Questionnaire		x				x				x
Adult Rejection Sensitivity Questionnaire		x				x				x
Multidimensional Scale of Perceived Social Support		x				x				x
BPI (pain)		x				x				x
PBI (parent bonding)		x								
Childhood Trauma Questionnaire		x								
Faces Discrimination Task		x								x
MRI scan (structural, SFT, Resting State, Pain Task)		x								x

[a] Vital signs include blood pressure and pulse

[b] Clinical labs include CBC, Chem 7, TSH, Cholesterol, B12, and Folate

[c] Pregnancy test will be performed on women of child bearing potential

[d] Washout period only for subjects on other antidepressant medication

* Assessment may be repeated based on clinician discretion; ** Optional

2.6. Tianeptine administration.

Following screening and baseline testing, all subjects will begin tianeptine 12.5 mg three times daily (total daily dose 37.5 mg/day) for a total duration of 8 weeks of treatment. Subjects who develop side effects that prevent them from taking the the full three times daily dosage will have their dosage reduced to tianeptine 12.5 mg twice daily, and those unable to tolerate at least 25 mg/day dosing will be dropped out of the study. Based on the extensive experience of clinicians in Europe, where tianeptine is approved for the treatment of depression, we expect this dosage regime to be well-tolerated. During the study, concomitant use of other antidepressants, antipsychotics, anticonvulsants, central nervous system stimulants, anti-addiction agents, and cognitive enhancers are prohibited, with the exception of small doses of benzodiazepines (≤ 2 mg lorazepam equivalents per day), which will be permitted for anxiety or insomnia.

Medication was purchased from Neuraxpharm in Germany and shipped to the NYSPI pharmacy where it is stored. Medication is shipped to the MSSM pharmacy, where it is packaged and prescribed for MSSSM patients in containers containing a 2 week supply (50 blister packed 12.5 mg pills – enough for two weeks plus an additional pills alloatted in case of a delayed visit) at the 0, 2,4, and 6 week visits and 20 blister packed pills for the final taper. Medication is shipped to the Stanford Depression Research Clinic in the same quantities and it is dispensed to patients using the same procedures as atMSSM. At each in person visit, the subject should return the bottle, and the number of remaining pills will be counted and recorded to monitor compliance.

2.7. Early discontinuation criteria and handling of emergencies.

The risk of non-response to tianeptine during the study period is addressed by having close clinical follow up of study subjects and stringent withdrawal criteria. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening in the judgment of the study clinician; (3) a CGI-Improvement rating[7] by the study clinician of 6 (worse) or 7 (much worse) for 2 consecutive visits; or (4) development of significant side effects or an adverse event grade 3 or higher. Any subject meeting any of these criteria will be withdrawn from the study and treated clinically. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments. If clinical worsening necessitates more intensive treatment, appropriate clinical care will be given but if possible the patient will still complete the ongoing assessments and final imaging visits.

Should a subject express suicidal ideation at any time during a study visit, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver (if available), referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

2.8. Tianeptine taper and post-protocol treatment.

Once all study assessments are completed, subjects will be tapered off of tianeptine medication. Subjects will have their dosage reduced to 12.5 mg twice daily for two weeks, then 12.5 mg once daily for two weeks, and then tianeptine will be discontinued. Subjects will be assessed every two weeks in this post-protocol phase, with continuation of HRSD and CGI rating

scales. Appropriate clinical options will be discussed with any subject demonstrating worsening HRSD (≥ 16 on 24-item scale) or CGI (Improvement score ≥ 5 or Severity score ≥ 4 for two consecutive weeks) scores, most likely including initiation of FDA-approved antidepressant medication.

2.9 References

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7) Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.

3. Subject Selection and Withdrawal

3.1 Inclusion Criteria

1) Age 21 – 60 years, male or female
2) Current diagnosis of Major Depressive Disorder (MDD) without psychotic features
3) 24-item Hamilton Rating Scale for Depression (HRSD) ≥ 16
4) At least two previous antidepressant treatment failures (adequate trials within current episode) with a SSRI, SNRI, bupropion, tricyclic antidepressant, mirtazapine, nefazodone, or monoamine oxidase inhibitor, or transcranial magnetic stimulation (TMS), or IV ketamine or nasal ketamine.
5) Capable of providing informed consent and complying with study procedures
6) Currently using or willing to use contraception, if woman of childbearing potential (such as condoms, IUD, or oral contraceptive), for duration of the study.

3.2 Exclusion Criteria

1) Any history of opioid-use disorder

2) Any history of moderate- non-opioid (except for Nicotine) substance-use disorder.
3) Any severity of alcohol use disorder (including mild)
4) Past or current psychosis, psychotic disorder (including psychotic MDD), mania, or bipolar disorder
5) Hamilton Rating Scale for Depression (HRSD) suicide item > 2 or Clinical Global Impressions (CGI)-Severity score of 7 at baseline
6) Previous or current treatment with Tianeptine
7) Current treatment or currently taking an opioid.
8) Failed depression treatment with electroconvulsive therapy.
9) Acute, severe, or unstable medical illness
10) Weight > 300 lbs, or girth size incompatible with scanner bore.
11) Any physical or intellectual disability adversely affecting ability to complete assessments. MMSE <26
12) for MSSM site - Having contraindication to MRI scanning (such as metal in body) or inability to tolerate the scanning procedures (e.g., severe obesity, claustrophobia)
13) Current pregnancy or currently breast feeding.
14) Abnormal baseline liver function tests
15) Currently being treated with an antidepressant medication, an antipsychotic or mood stabilizer.

a) If a participant is taking a protocol dis-allowed medication at the time of screening and despite medication treatment still meets the inclusion criteria of an HRSD>16, the participant may discontinue the medication under the supervision of their treating physician or the study clinician.

16) Positive urine toxicity at screening (except for cannabinoid)

4. Primary Study Endpoints

1. HRSD change from Week 0 to Week 8

4.1 Secondary Study Endpoints

1. Response rate to tianeptine (baseline HRSD decreases by ≥ 50%)
2. Remission rate to tianeptine (final HRSD ≤ 7)
3. Change in VAS pain scores from Week 0 to Week 8
4. Change in emotional pain as measured by the ARSQ from Week 0 to Week 8

4.2 Primary Safety Endpoints

The primary safety endpoint is:

Rate of serious adverse events (SAEs):
All SAEs will be assessed by a study physician to determine whether the relationship to the study procedures or treatment is considered to be likely, unlikely or unknown.

5. Statistical Plan

5.1 Sample Size Determination

With total sample size of 75 subjects, we have >80% power to detect an effect size for a change in HRSD (from week 0 to week 8) of at least (Cohen's) d = 0.33 (small-medium), using a 2-sided test with a 5% significance level. With this sample size we can construct 95% confidence intervals for the response/remission rates that are no more than 25 percentage points wide. For our subgroup analyses to examine the hypothesis that baseline pain (physical or emotional) will differentially relate to improvement in depression, assuming a median split (low/high, n = 37/38) for a given physical or emotional pain battery score, we have >80% power to detect an effect size for a difference in change in HRSD (low group vs. high group) of at least d = 0.66 (medium-large), using a 2-sided test with a 5% significance level. Similarly, we have >80% power to detect differences in proportions of responders/remitters between the pain groups that are at least 30 percentage points. As an example, if depression response/remission is 10% in the low pain group and 40% in the high pain group, we have 86% power to find this statistically significant at the 5% significance level.

5.2 Statistical Methods

Descriptive analyses for all variables collected at all time points will be conducted both overall and by study site. If differences are found between the study sites on outcomes of interest, then study site will be adjusted for in the analyses. For the intent-to-treat sample (i.e. those who started on drug at week 1 regardless of compliance across the 8 weeks), we will report proportions of responders and remitters and mean changes in HRSD, VAS pain score, and ARSQ from week 0 to week 8. In addition to these point estimates, we will report the corresponding 95% confidence intervals. Similar analyses will be done on the sample of completers (i.e. those who complied with drug administration across all 8 weeks based on pill counts of at least 80%).

To examine the hypothesis that baseline pain level will be predictive of response to tianeptine, we will further investigate whether any single baseline pain battery score can be used to construct subgroups of subjects showing greater response to tianeptine. Based on the distribution of a given pain battery score and preliminary exploratory bivariate modelling, we will dichotomize the pain score (low/high) and compare response/remission rates and change scores for HRSD between the groups corresponding to low and high pain battery score. We will

report effect sizes corresponding to differences in response/remission rates and differences in HRSD change scores. Exploratory analyses will employ multivariable logistic (for response/remission outcomes) and linear (for HRSD change score) regression to investigate whether combinations of baseline pain scores can be used to identify subgroups who will show greater response to tianeptine. Additional analyses will employ multivariable logistic and linear regression to investigate associations between baseline neuropsychiatric and/or MRI measures and remission/response or HRSD change score. To take advantage of the fact that HRSD and TESS are collected at each study visit (8 post-baseline measures), we will also employ linear mixed effects models to investigate the effects of each baseline pain battery score on HRSD and TESS over time.

5.3 Subject Population(s) for Analysis

Subjects will be adult outpatients with treatment-resistant MDD who are without contraindications for neuroimaging procedures or tianeptine administration.

6. Safety and Adverse Events

6.1 Definitions

Adverse Event: *Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event: *Serious adverse event* or *serious suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse Event Reporting Period: The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment followup. For this study, the study drug follow-up is defined as 24 hours following the last administration of study drug (or the end of the study for those who must stop tianeptine but continue with the assessments).

Preexisting Condition: A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings: At screening, any clinically significant abnormality will be documented. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Abnormal Laboratory Values: A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met: (1) the laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality, (2) the abnormality suggests a disease and/or organ toxicity, (3) the abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery: Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances: (1) Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition, (2) hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, (3) hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Known Side Effects of tianeptine:

Tianeptine is generally well tolerated and severe side effects are rare.[1-5] Tolerability in comparative clinical trials has been generally found to be better than tricyclic antidepressants and comparable to selective serotonin reuptake inhibitors.[1-5] Commonly reported side effects with an incidence between 1 and 10% include the following:[1-6]

Gastrointestinal: nausea, vomiting. flatulence, constipation, abdominal pain, dry mouth, loss of appetite

Psychiatric and Central Nervous System: headache, dizziness, altered dreaming, drowsiness, insomnia, presyncope, tremors

Cardiovascular: palpitations, chest pain, hot flashes, tachycardia

Respiratory: difficulty breathing

Musculoskeletal: muscle pain, lower back pain

General: feeling of weakness, feeling of lump in the throat

6.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events (AEs) by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal

diagnostic procedures results will be recorded in the source document. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome.

6.3 Reporting of Serious Adverse Events

6.3.1 IRB Notification by Investigator

Each SAE will be reported by the site within 24 hours to their IRB as well as to the IND sponsor by email to: jaj2@cumc.columbia.edu. The site PI together with the IND sponsor will make the determination as to whether an incident, experience or outcome is likely to be the result of study procedures or treatment. The investigator must conclude in the SAE Report whether the protocol and/or consent form(s) should be modified as the result of the SAE. If the protocol and/or consent document(s) requires a revision, a modification must be submitted. At the time of continuing review of a protocol by each site's IRB, the site PI will submit a summary of all SAEs that occurred during the review period and since the beginning of the study, with a copy to the IND sponsor.

6.3.2 FDA Notification by Sponsor

The IND sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the investigator's original
receipt of the information. All other events that are considered to be serious, unexpected and possibly related to the study drug will be reported to the FDA within 15 calendar days. In addition, the IND sponsor will provide a summary of all SAEs in the annual reports submitted to the FDA.

6.4 Drug Related Risks

Tianeptine is generally well tolerated and severe side effects are rare.[1-5] Tolerability in comparative clinical trials has been generally found to be better than tricyclic antidepressants and comparable to selective serotonin reuptake inhibitors.[1-5] Commonly reported side effects with an incidence between 1 and 10% include the following:[1-6]

Gastrointestinal: nausea, vomiting. flatulence, constipation, abdominal pain, dry mouth, loss of appetite

Psychiatric and Central Nervous System: headache, dizziness, altered dreaming, drowsiness, insomnia, presyncope, tremors

Cardiovascular: palpitations, chest pain, hot flashes, tachycardia

Respiratory: difficulty breathing

Musculoskeletal: muscle pain, lower back pain

General: feeling of weakness, feeling of lump in the throat

Extremely rarely, hepatotoxicity may occur, which is evidenced by increased liver enzymes and is fully reversible on drug withdrawal.[7-9] Such liver toxicity appears to result from an immunoallergic response to the drug. To our knowledge, only 3 such cases have been reported in the literature. In contrast, the hepatic safety of tianeptine appears excellent in the vast majority of patients, even in instances of excessive consumption during abuse. For instance, a patient who became addicted to tianeptine and consumed doses of up to 1875 mg/day for over 5 months experienced no changes in hepatic toxicology parameters.[10] Liver function tests will nonetheless be repeated at Week 4 to insure that levels are stable.

When used at the usual dosage of 37.5 mg/day, there is no development of physical or psychological dependence on tianeptine and no notable withdrawal symptoms on treatment cessation.[1-5] Rarely (1-3 per 1000)[11], abuse of tianeptine or dependence on the drug (when used at supratherapeutic doses) may occur. To account for this risk, we have planned for abuse risk mitigation by excluding patients with a history of opioid abuse, limiting drug distribution to 9-day courses provided at weekly clinical visits, and monitoring compliance at each clinical visit.

Drug Dependence and Abuse Potential:

Tianeptine's activity is a full agonist of the mu-opioid receptor (MOR; its hypothesized mechanism of action) and the use of the drug in clinical practice has been safe. The tianeptine dose (12.5 mg, t.i.d.) that is used clinically for depression is in the sub-euphoric range, that is, the drug does not induce notable rewarding or psychoactive (other than anti-depressant) effects at this dose. The clinically used dose is also not associated with physical or psychological dependence after discontinuation, even after prolonged treatment. Therefore, there appears to be a significant safety margin between the therapeutic dose and the dose necessary to induce acute rewarding or other psychoactive effects. In a controlled trial of abuse liability in healthy volunteers, a single supratherapeutic dose of tianeptine (75 mg) did not separate from placebo in any subscale of the Addiction Research Center Inventory, in contrast to the positive control methylphenidate (40 mg), suggesting limited, if any, abuse or addiction liability at typical therapeutic doses. Consistent with this finding, abuse of tianeptine was not observed during treatment of patients previously addicted to opioids, suggesting that in most cases the clinical dose is too low to reinitiate drug seeking behavior in patients with a history of substance abuse. Using incidence of "doctor shopping" as an indicator of aberrant use, another study found that

tianeptine abuse potential is comparable to or slightly lower than that of benzodiazepines, drugs widely used in clinical practice despite recognized modest abuse potential. Accordingly, the risk-benefit ratio for use of tianeptine in psychiatric indications is favorable, especially for treatment-resistant depression, where standard-of-care treatments have already failed.Despite this occasional incidence of serious misuse, acute tianeptine overdose or chronic abuse are not often associated with severe complications or fatalities. In a single ascending dose study in healthy volunteers, the high dose of 337.5 mg elicited only transient adverse effects of nausea, vomiting, and sedation.

Accordingly, there is expected to be limited risk of dangerous overdose in the present study. Similarly, most chronic users of high-dose tianeptine do not experience serious toxicological complications (notably, no hepatotoxicity except in extremely rare cases) other than a withdrawal syndrome on discontinuation. In a long-term treatment study, 7 patients who attempted suicide by tianeptine overdose (dose of 150-500 mg, concomitant with alcohol or other psychotropic drugs) survived with favorable outcomes. Overdose has also been reported to be reversible with naloxone, consistent with agonist activity at MOR. To our knowledge, only 5 overdose deaths following tianeptine ingestion have been reported in the literature. In one case, tianeptine was the only intoxicant identified. However, the other cases were complicated by the identification of other psychoactive substances in the circulation of the decedents (one in combination with tramadol, one in combination with alprazolam, one a suicide in combination with alcohol, and one a suicide in combination with clomipramine and hydroxyzine).

To minimize risk patients with any history of opioid-use disorder or any history of moderate non-opioid (except nicotine) substance use disorder are excluded. Medication is distributed biweekly with a two week supply given and unused pills are collected at each in-person visit.

References

(1) McEwen, B. S.; Chattarji, S.; Diamond, D. M.; Jay, T. M.; Reagan, L. P.; Svenningsson, P.; Fuchs, E. The Neurobiological Properties of Tianeptine (Stablon): From Monoamine Hypothesis to Glutamatergic Modulation. *Mol. Psychiatry* **2010**, *15* (3), 237–249.

(2) Kasper, S.; McEwen, B. S. Neurobiological and Clinical Effects of the Antidepressant Tianeptine. *CNS Drugs* **2008**, *22* (1), 15–26.

(3) Wagstaff, A. J.; Ormrod, D.; Spencer, C. M. Tianeptine: A Review of Its Use in Depressive Disorders. *CNS Drugs* **2001**, *15* (3), 231–259.

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(5) Wilde, M. I.; Benfield, P. Tianeptine: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Depression and Coexisting Anxiety and Depression. *Drugs* **1995**, *49* (3), 411-439.

(6) See the Summary of Product Characteristics (SmPC) included with this submission as Attachments E (original German) and F (English translation).

(7) Balleyguier, C.; Stérin, D.; Ziol, M.; Trinchet, J. C. Acute Mixed Hepatitis Caused by Tianeptine [Article in French]. *Gastroenterol. Clin. Biol.* **1996**, *20*, 607-608.

(8) Le Bricquir, Y.; Larrey, D.; Blanc, P.; Pageaux, G. P.; Michel, H. Tianeptine – An Instance of Drug-Induced Hepatotoxicity Predicted by Prospective Experimental Studies. *J. Hepatol.* **1994**, *21*, 771-773.

(9) Rifflet, H.; Vuillemin, E.; Rifflet, I.; Oberti, F.; Pilette, C.; Calès P. Acute Painful and Febrile Hepatic Involvement Related to Ingestion of Tianeptine [Article in French]. *Gastroenterol. Clin. Biol.* **1996**, *20*, 606-607.

(10) Vandel, P.; Regina, W.; Bonin, B.; Sechter, D.; Bizouard, P. [Abuse of Tianeptine. A Case Report]. *Encephale.* **1999**, *25* (6), 672–673.

(11) "Stablon 12.5 mg, coated tablet, Re-assessment of Actual Benefit at the request of the Transparency Committee" Haute Authorité de Santé; Transparency Committee Opinion; December 5th, 2012.

6.5 Stopping Rules

Refer to Section 2.7

6.6 Medical Monitoring

Adverse events will be documented in the study database. Notification of SAEs to the IRB and FDA will take place as described in Section 6.3. All adverse events will be reviewed and assessed by the study investigators at each site, and the SAEs from each site will be reviewed by the IND sponsor.

7. Data Handling and Record Keeping

7.1 Confidentiality

All study data will be collected and stored in compliance with all applicable guidelines regarding patient confidentiality and data integrity. All

subject research data will be coded with subject ID number. All laboratory and clinical information obtained from this research will be maintained in locked offices and will be accessible only to the main investigators of this project. The REDCAP-based electronic database used during the trial is secure and password protected. Subjects' information will not be discussed in any form in the presence of other subjects or non-study personnel. Subjects will only be referred to by their subject unique ID number in all study documents. For every research subject, relevant clinical information is documented on electronic case report forms and source documents and stored in the secure electronic database or in a double locked area. All study records will be maintained for a minimum of 7 years. If requested, the IRB and FDA will have full access to all study records.

7.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other
activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include: research clinic charts, laboratory data,
pharmacy dispensing records, MRI scans, and results of physiologic testing.

7.3 Case Report Forms

The study will utilize both paper case report forms (CRFs) and an electronic data capture system (EDC) Acquire EDC ™ for data collection (see below). Paper case report forms and supporting source documents will be filed in the subject charts and will be the basis for data entered into Acquire. All data requested on the paper CRFs must be recorded, and all missing data must be explained. If a field on the paper CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialed and dated.

The study statisticians will make regular reports to investigators on accrued data, identify unusual or unexpected data points, and request that they be confirmed or corrected. The data will be queried and monitored in accordance with Attachment L, the "Study Monitoring Plan," with a frequency specified in the plan and based on study progress and need.

The Innovative Clinical Research Solutions (ICRS) group at the Nathan S. Kline Institute for Psychiatric Research (NKI) will design the eCRFs to capture all required protocol information and will host the database. ICRS personnel have been providing databases and management support for clinical

research studies for over 35 years and have conducted such functions for numerous studies funded by the National Institute of Mental Health (NIMH) and by pharmaceutical companies (FDA-regulated IND studies) .

The primary objectives of the ICRS data management methodology are to insure the completeness and integrity of all study data. To accomplish these objectives, ICRS will provide a comprehensive data collection methodology combined with strong planning, control, and coordination with study research staff. ICRS will develop all study electronic Case Report Forms (eCRFs) to standardize data collection. A comprehensive web-based data acquisition and management system, Acquire, will be programmed to process, edit and store all study data in a centralized database. Acquire will be developed to meet the specific requirements of the study. ICRS personnel will implement rigorous data editing/validation using the Acquire system to insure the highest possible level of data accuracy.

A description of the Acquire EDC system is contained in Attachment M.

Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) has been created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non- serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects.

This protocol's DSMB consists of 4 members:

The DSMB includes Connor Liston MD/PhD from Cornell (chair), Martin Keller MD from Brown, Sam Wilkerson MD from Yale, and Charles Green PhD (statistician) U. of Texas at Houston

The study team will provide the DSMB with reports biannually containing the following information for review:

- Summary of overall study progress
- Subject enrollment, treatment retention and dropout
- Serious adverse events (SAEs)
- Non-serious adverse events (AEs)

As highlighted in the SAE section of this MOP, expedited review will occur for all SAEs by the DSMB in addition to the regular biannual review/meeting. The study team must report the SAE within 48 hours of obtaining knowledge of the SAE. Further details are explained in the SAE section of this MOP.