A Preliminary, Double-Blind, Placebo-Controlled Trial of the Effect of Glucocorticoid Receptor Antagonist Treatment on Biologic and Symptom Outcomes in Patients with Borderline Personality Disorder and Histories of Childhood Abuse

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Alan Breier, MD
Department of Psychiatry, Indiana University

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1.0 Background

Borderline personality disorder (BPD) is a major mental illness, which is both prevalent and disabling. BPD is present in up to 18% and 25% of individuals in inpatient and outpatient psychiatric settings, respectively (1). According to recent findings, this disorder occurs in nearly 6% of the general population (2). Patients with BPD demonstrate extensive psychopathology which spans multiple symptom domains, including affective dysregulation, anxiety, impulsivity, self-injurious behaviors, psychosis (paranoia and hallucinations), dissociation, and chronic interpersonal difficulties. Also, up to 84% of patients make some form of suicide attempt, and up to 10% complete suicide (1). While individuals with BPD may present a superficially intact social façade, they often under-achieve, feel miserable, and lead very troubled lives. Furthermore, high percentages of BPD patients suffer from comorbid psychiatric illnesses (1), such as major depression (50%), dysthymia (70%), bipolar disorder (9-11%), post-traumatic stress disorder (40%), substance use disorders (35%), and eating disorders (5-20%). BPD worsens the clinical course of co-occurring Axis I disorders and limits their treatment responsiveness. For example, Gunderson et al. (2004) found that the presence of BPD significantly reduced the rate of major depressive disorder (MDD) remissions. In this study, remissions of BPD symptoms frequently were followed by MDD remissions (3). BPD is a substantial and often unaddressed barrier to lessening the individual, family, and societal burden of other severe mental illnesses.

Substantial progress has been made in the development and empirical validation of specialized psychotherapies for BPD (1). These specific approaches address BPD based upon their respective theories of the etiology and the psychological underpinnings of the illness. Currently, pharmacotherapy plays a prominent role in BPD clinical management. In contrast to the specialized psychotherapies, available psychotropic agents were not designed for BPD and are seemingly more suited to other psychiatric populations. BPD patients are exposed to the marked costs and side effects of medications in the face of often minimal symptom amelioration. To date, no medication treats BPD as a whole (1). BPD patients need similarly specialized pharmacotherapy options, which are guided by neurobiological hypotheses and experimental findings regarding BPD's particular pathophysiologic mechanisms.
While the development of BPD is multi-determined, childhood abuse and neglect are major risk factors. In a large study of patients with BPD, 91% endorsed abuse histories, and 92% reported histories of being neglected before 18 years of age (4). Lasting neurobiological effects of this childhood adversity may contribute to BPD pathophysiology in adulthood. One such effect could be hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Indeed, Rinne et al. (2002) observed a hyper-responsive HPA axis (enhanced ACTH and cortisol release following dexamethasone/corticotrophin-releasing hormone (CRH) challenge) in individuals with BPD and histories of sustained childhood abuse (5). Specifically, abused BPD patients appear to demonstrate a heightened CRH drive (6). Many BPD symptoms seemingly reflect stress sensitivity and coping deficits. Ongoing HPA axis hyper-responsiveness via elevated CRH drive may be a neurobiological substrate for the stress response impairment underlying recurrent BPD phenomenology, such as self-injury (cutting, burning, head banging, etc.), suicidality, dissociation, psychosis, extreme emotional reactivity, rage, and aggression. These are the symptoms which currently compel clinicians to turn to available medications, often with limited improvement. A drug that specifically counteracts excessive CRH drive might directly target stress-related symptoms in individuals with BPD and histories of childhood trauma.

Mifepristone is an antagonist of type II glucocorticoid (GR-II) receptors, which has shown safety, efficacy, and good tolerability in the treatment of psychotic major depression (PMD). Like BPD, HPA axis hyper-responsiveness appears to play a role in PMD pathophysiology (7). Belanoff et al. (2002) hypothesized that mifepristone causes a normalizing "resetting" of HPA axis rhythm, accounting for its efficacy in PMD (8). Mifepristone produces a marked (2- to 3- fold) compensatory increase in central cortisol levels via its antagonism of GR-II receptors. This consequent central cortisol elevation may then

be able to counteract abnormally heightened CRH activity via enhanced negative feedback mechanisms (7). Pronounced antagonism of hippocampal GR-II receptors by mifepristone may hyper-sensitize these receptors. This effect can then reestablish the negative feedback capacity of cortisol at hippocampal GR-II receptors to down-regulate HPA axis activity, as the hippocampus modulates hypothalamic function. Notably, prior research suggests that this postulated "rebalancing" of HPA axis hyperactivity (CRH overdrive) by mifepristone via central GR-II receptor blockade may persist after the discontinuation of active drug treatment. In clinical studies investigating mifepristone treatment of patients with either bipolar disorder or schizophrenia, a sustained significant decrease in peripheral cortisol level, as compared with pretreatment baseline, was observed 14 days after the discontinuation of mifepristone, which had been administered at 600 mg/day for 7 days (9). There was no significant change in cortisol level with placebo. Furthermore, previous trials of mifepristone for PMD preliminarily suggest that this agent may produce durable treatment effects on clinical symptoms which persist beyond the active drug therapy period. For example, in a large placebo-controlled trial, DeBattista et al. (2006) found that mifepristone led to significantly greater improvement of general psychiatric symptoms and positive psychotic symptoms in subjects with PMD after 7 days of active treatment which persisted to day 28 (following drug discontinuation after day 7). The significant antipsychotic benefits of mifepristone compared with placebo at day 7 appeared to persist up to day 56 (7 weeks after drug discontinuation). In this PMD trial, antidepressant benefits (at a trend level of significance) favoring mifepristone were seen at the day 56 outcome point (10). This durable (sustained) symptom benefit also was observed in an earlier open-label study of mifepristone for PMD. Significant improvements in measures of general psychiatric and depression symptomatology were reported at weeks 4 and 8 compared with pretreatment baseline levels following a circumscribed 6-day period of mifepristone administration (11).

In sum, elevated CRH activity appears to be present in BPD (6), suggesting that mifepristone may be a more targeted pharmacotherapy approach for stress-related BPD symptoms involving HPA axis dysfunction. Mifepristone may therapeutically dampen CRH overdrive in abused BPD patients. In a recent study, rats exposed to a preclinical model of developmental trauma, namely early maternal separation (MS), manifested heightened HPA responsiveness to a stress paradigm and associated cognitive impairment on laboratory measures. This cognitive impairment was ameliorated by mifepristone administration in the rats exposed to early MS (12).

2.0 Rationale

This is a proof of principle study of mifepristone in the treatment of individuals with BPD and histories of childhood abuse, which aims to translate neurobiological research concerning HPA axis abnormalities in BPD into a novel clinical intervention for patients. This project will also explore an innovative approach to the structure of pharmacotherapy for BPD. Specifically, we will employ the circumscribed (finite) drug administration period used in prior studies of mifepristone in neuropsychiatric illness, which differs from the current clinical practice of indefinite daily usage of medications. We hypothesize that mifepristone will beneficially impact stress response neurobiology and consequently ameliorate associated BPD symptoms.

3.0 Specific Aims

Specific aim 1: to evaluate whether mifepristone will produce rapid symptom reduction after seven days of active treatment, as measured by Borderline Personality Disorder Severity Index (BPDSI) total score. Further, to evaluate whether seven days of mifepristone treatment will result in a durable improvement in symptoms persisting after active treatment discontinuation, as measured by Borderline Personality

Disorder Severity Index (BPDSI) total score.

Specific aim 2: to evaluate safety and tolerability of mifepristone

Specific aim 3: to assess cortisol levels as a potential biomarker of HPA-axis engagement.

Exploratory Aims: to assess clinical and demographic moderators of response to mifepristone, including childhood abuse characteristics (e.g., type of abuse, age of onset, duration) and comorbid psychiatric illnesses.

Outcome Measures: The primary outcome measures will be the Borderline Personality Disorder Severity Index (BPDSI) total score. With this measure, we will be able to investigate specifically the effect of mifepristone on BPD's entire psychopathologic spectrum. For inclusion, all subjects must demonstrate a minimum severity of a total score $\geq$ 3 on the CGI-S. Secondary outcomes will include the BPDSI symptom domain subscales, the Brief Psychiatric Rating Scale (BPRS), the self-report Borderline Checklist , the Symptom Checklist-90-Revised (SCL-90-R), improvement in metacognitive capacity, and the Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) measures. Clinical assessments will be performed by trained raters, who will be blind to subjects' treatment condition.

4.0 Study Design

This is a single site safety and proof of concept study conducted at the Indiana University Psychotic Disorders Program. Twenty four subjects with borderline personality disorder will be randomized 1:1 to double-blind treatment with oral mifepristone or matched placebo for duration of seven days, with a follow up period.

5.0 Study Population (Inclusion/Exclusion Criteria)

Inclusion Criteria:

1. 18-64 years of age at study entry
2. Female or Male
3. DSM-IV-TR diagnosis of borderline personality disorder (confirmed by SCID II) with history of abuse prior to the age of 18.
4. Able to provide informed consent
5. Inpatient or outpatient
6. Clinical stability as defined by:
    a. Subjects must not have experienced an exacerbation of their illness within 4 weeks prior to randomization, leading to an intensification of psychiatric care in the opinion of the principal investigator. Examples of intensification of care include, but are not limited to: inpatient hospitalization, day/partial hospitalization, outpatient crisis management, or psychiatric treatment in an emergency room AND
    b. Psychotropic treatment stability for at least 2 weeks prior to randomization (no change in dosing or addition of any new psychotropic medication)
7. Female subjects of childbearing potential must test negative for pregnancy at screening visit and agree to use the double-barrier method, as defined by 2 physical barriers such as a condom, diaphragm, or cervical occlusive cap, coupled with an additional barrier such as spermicidal foam, gel, film, cream or suppository for the duration of the study. Subjects having undergone a

hysterectomy or bilateral oophorectomy or other form of female sterilization or patients having been medically confirmed to be post-menopausal, would not require any other method of contraception.
8. Minimum severity of a total score $\geq$ 3 on the CGI -S
9. Must agree not to consume tonic water and grapefruit or grapefruit product for 3 days prior to beginning medication and until the final study visit

Exclusion Criteria:
1. DSM-IV TR diagnosis of (confirmed by SCID) schizophrenia or a related psychotic disorder, bipolar I disorder, or dementia
2. Subjects who are considered prisoners per the Indiana University Standard Operating Procedures for Research Involving Human Subjects.
3. Subjects with current acute, serious, or unstable medical conditions, including, but not limited to: inadequately controlled diabetes, asthma, COPD, severe hypertriglyceridemia, recent cerebrovascular accidents, acute systemic infection or immunologic disease, unstable cardiovascular disorders, malnutrition, renal gastroenterologic, respiratory, endocrinologic (particularly illnesses related to the HPA-axis, e.g., Cushing's Syndrome), neurologic, hematologic, or infectious diseases
4. Clinically significant electrocardiogram (ECG) abnormality prior to randomization including: subjects with a corrected QT interval (Bazett's; QTcB) > 450 msec (male) or >470 msec (female) prior to randomization (based on the cardiologist overread). Repeat ECGs will be conducted at the discretion of the principal investigator or medical designee
5. Use of any exclusionary medication listed in Attachment 2: Concomitant Medication.
6. Pregnant or lactating women or women who plan to become pregnant or will be lactating within one month after cessation of study medication
7. Known IQ <70 based on medical history
8. Currently using an intrauterine device (IUD)
9. History of treatment with mifepristone or any mifepristone-containing medication at any time
10. Known history of (1) Hepatitis C virus antibody, (2) Hepatitis B surface antigen (HBsAg) with or without positive Hepatitis B core total antibody, or (3) HIV 1 or 2 antibodies
11. Subjects with moderate to severe renal impairment as defined by creatinine clearance (CrCl) < 60 ml/min (measured by the Cockcroft-Gault equation) at screening
12. Subjects with hepatic impairment as defined by liver transaminases or total bilirubin > 3 × upper limit of normal (ULN)
13. Subjects considered a high risk for suicidal acts, as determined by the principal investigator.
14. Subjects who have participated in a clinical trial with any pharmacological treatment intervention for which they received study-related medication in the 4 weeks prior to screening OR Subjects currently receiving treatment (within 1 dosing interval plus 4 weeks) with an investigational depot formulation of an antipsychotic medication
15. Subjects who demonstrate overtly aggressive behavior or who are deemed to pose a homicidal risk in the principal investigator's opinion
16. Psychosocial treatment changes 14 days prior to randomization
17. History of unexplained vaginal bleeding, endometrial hyperplasia with atypia, or endometrial carcinoma

6.0 Subject Recruitment

Subjects will be recruited through referring community mental health centers, treatment providers, invited to participate if they are included in our registry, and self-referrals through advertisement and word-of-mouth.

7.0 Study Procedures

See Study Procedures Table (Attachment 1)

8.0 Clinical Assessments and Procedures

The following assessments will be administered at one or more visits during the duration of the study according to the study procedures tables (Attachment 1). All assessments will be completed by study personnel based on interviews with the subject or based on questionnaires completed by the subject.

Diagnostic Interviews

The Structured Clinical Interview for DSM-IV-TR (SCID-I/P Patient Edition) will be used to confirm the diagnosis of Axis I disorders and rule out schizophrenia or a related psychotic disorder or bipolar I disorder (18). The SCID-IP is a semi-structured interview designed to evaluate DSM-IV-TR Axis I diagnoses.

The Structured Clinical Interview for DSM-IV AXIS II (SCID-II) Personality Disorders Version will be used to confirm a borderline personality disorder diagnosis (17).

The Brief Psychiatric Rating Scale (BPRS)
The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms (19). Some of the items (e.g. mannerisms and posturing) can be rated simply on observation of the subject; other items (e.g. anxiety) involve an element of self-reporting by the subject.

Clinical Global Impressions Severity Scale (CGI-S)
The CGI-S will be used for repeated evaluations of global psychopathology (20-21). The CGI-S scale is widely used in schizophrenia research and is a single 7-point Likert scale rating severity of psychopathology on a scale of 1 (normal, not ill) to 7 (very severely ill).

Clinical Global Impressions Severity Improvement Scale (CGI-I)
The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point Likert scale, ranging from very much improved (1) to very much worse (7) (20-21).

Interview for Traumatic Events in Childhood (ITEC)
The ITEC aims to assess multiple types of childhood traumatic events, including sexual abuse, physical abuse, emotional abuse, and neglect (22). The ITEC utilizes an empirically based scoring system for determining the severity of traumatic events. Each subscale yields a composite score indicating the severity of maltreatment. An abbreviated version may be used at the discretion of the principal investigator.

Indiana Psychiatric Illness Interview (IPII)
The IPII is a semi-structured interview developed to assess illness narratives. Study personnel conduct the interview, which typically lasts between 30 and 60 minutes (26). Responses are audio taped and later transcribed. The interview is divided conceptually into four sections. First, rapport is established and subjects are asked to tell the story of their lives in as much detail as they can. Second, subjects are asked if they think they have a mental illness and how they understand it. This is followed with questions about what has and has not been affected by their condition in terms of interpersonal and psychological life. In the third section, subjects are asked if and how their condition "controls" their life and if and how they

"control" their condition. Fourth, subjects are asked what they expect to stay the same and what will be different in the future.

Borderline Personality Disorder Severity Index (BPDSI)-90 day Version
The BPDSI is a semi-structured clinical interview assessing the frequency and severity of manifestations of Borderline Personality Disorder during a circumscribed period of three months. All frequency questions are scored on 10-point scales (0 = never; 10 = daily). This also applies to the items where such a high frequency is unlikely (14).

Borderline Personality Disorder Severity Index (BPDSI)-7 day Version-Modified
The BPDSI is a semi-structured clinical interview assessing the frequency and severity of manifestations of Borderline Personality Disorder during a circumscribed period of the previous 7 days. All frequency questions are scored on 7-point scales (0 = never; 7 = daily). This also applies to the items where such a high frequency is unlikely. This modified version was created with the developer of the BPDSI, Dr. Arnoud Arntz. The modified 7 day version will be used as one measurement of BPD symptom changes during the course of the study (14).

Symptom Checklist-90-R (SCL-90-R)
The SCL-90-R instrument helps evaluate a broad range of psychological problems and symptoms of psychopathology. The instrument is also useful in measuring patient progress or treatment outcomes. The SCL-90-R contains 90 items on a 5-point rating scale yielding nine scores along primary symptom dimensions and three scores among global distress indices (16).

BPD Checklist
The BPD Checklist is a DSM-IV based self-report questionnaire, designed to assess the experienced burden of specific BPD symptoms during the previous month (23).

9.0 Safety Assessments and Procedures

Vitals
Vital signs will be assessed at study visits per Study Procedures Table (Attachment 1). Blood pressure and heart rate will be taken in a seated or supine position after a rest period of five minutes.

Medical History
The subject's lifetime medical history will be taken during the screening period. Medical history includes previous and current diseases.

Physical Examination
A physical examination will be performed including a neurological examination.

Electrocardiograph (ECG)
Triplicate supine, 12 lead ECGs will be performed according to the Study Procedures Table (Attachment 1).

10.0 Laboratory Assessments

Laboratory assessments (blood and urine) will be collected at time points specified in Study Procedures Table (Attachment 1) and analyzed by a local laboratory with the exception of the urine dipstick

assessments which will be collected and analyzed onsite.
A total of ~16ml of blood will be collected for screening assessments (Visit 1), ~28ml will be collected at baseline (Visit 2), ~17ml will be collected at Day 7 (Visit 4), ~12ml will be collected at Day 14 (Visit 5), and ~22ml will be collected at Day 28 (Visit 6).

Laboratory assessments to be completed:
Complete Blood Count with differential (CBC w/diff)
Comprehensive Metabolic Panel (CMP)
Pregnancy testing: serum and urine
Cortisol (must be drawn +/- 30 minutes of initial Visit 2 draw time)
Pharmacokinetics
Optional Biobank blood sample

Pharmacokinetics
Six ml of blood will be collected for trough mifepristone plasma concentration analysis (sent for analysis to MicroConstants in San Diego, CA).

Optional Biobank Blood Sample
An additional 10ml of whole blood will be collected (at Visit 2 and Visit 6) and sent to the Indiana Clinical and Translational Sciences Institute (CTSI) from all subjects who sign a separate consent and will be stored for later analyses, such as genetic examination. Subjects may refuse to participate in the repository without consequence to their participation in the main study. Non-identifying demographic information will be submitted to the CTSI at the time of sample submission. Subjects will be able to request sample destruction from the CTSI repository by formal request to the main study site.

11.0 Criteria for Rescreening, Repeat Assessments, and Discontinuation

Repeat Assessments
Screening assessments can be repeated within the screening window under the same screening number with the exception of eligibility criteria related rating scales/questionnaires. Subject diagnosis confirmation will not be repeated.

Rescreening
Subjects who screen fail may be rescreened one time, under a new screening number. If a subject is rescreened, all screening assessments (with the exception of the diagnosis confirmation) must be repeated and the stability criteria timelines must be met.

Discontinuation
Subjects will be discontinued from the active treatment phase under the following circumstances:

1. Any psychosocial treatment changes
2. Suicide attempt
3. Missing 2 or more doses of study medication
4. Becoming pregnant
5. Developing a serious infectious disease
6. Have a change in stability criteria indicated in inclusion criteria #6
7. Subjects who require treatment with any excluded concomitant medications (See Attachment 2)

If subjects discontinue from the study, discontinuation assessments will be at the discretion of the

principal investigator.

A subject may withdraw from the study medication at any time at her own request, or may be withdrawn at any time at the discretion of the principal investigator for safety, behavioral, or administrative reasons.

12.0 Study Medication

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate. Placebo tablets will look like mifepristone tablets, with matching shape, taste, and color. Mifepristone and matching placebo will be obtained from the manufacturer, Danco Laboratories in New York, NY. Study medication will be stored according to the details on the product label.

Dosing
The dosing used in this study is 600 mg by mouth once daily (see package insert for more information).

Compliance
Compliance will be assessed at each visit by direct questioning and medication count of unused medication and packaging to be returned at each visit. Adequate study medication dispensing records will be obtained.

13.0 Concomitant Medication

See Concomitant Medication Table Attachment 2

14.0 Adverse Events/Risks

For the purposes of collecting and evaluating all information found during this clinical study, an **adverse event** is any undesirable or unexpected experience that occurs after informed consent has been obtained without regard to the possibility of a causal relationship, and without regard to treatment group assignment. All adverse events will be documented and all serious adverse events will be reported following local Institutional Review Board (IRB) requirements.

For non-serious adverse events, research staff will question each subject and will document the occurrence and nature of presenting condition(s). Pre-existing condition(s) and any change in the pre-existing condition(s) will be documented and/or the occurrence and nature of any adverse event. Adverse events (AEs), especially those for which the relationship to study medication is not "unrelated," will be followed up until they have returned to baseline status or stabilized at the discretion of the principal investigator. If after the follow-up period, return to baseline or stabilization cannot be established an explanation will be recorded in the source documentation.

The most common adverse events include:

- Nausea
- Vomiting

- Decreased appetite
- Diarrhea
- Fatigue
- Headache
- Dizziness
- Arthralgia
- Back pain
- High blood pressure

Females only:

- Endometrial hypertrophy
- Uterine cramping
- Vaginal bleeding

A **serious adverse event** is any adverse drug experience occurring at any dose that: results in death, is life threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, or results in congenital anomaly/birth defect.

The following were considered serious adverse events in people with Cushing's syndrome and medical termination of pregnancy:

- Adrenal insufficiency
- Hypokalemia
- QT interval prolongation

It's not clear how frequently these serious adverse reactions may occur in an individual with BPD who does not have Cushing's syndrome and is not pregnant. This is because the vast majority of available safety data from clinical trials is for individuals with Cushing's syndrome or for women who used this medication for the termination of pregnancy and there is very little data available for people with neither condition.

Mifespristone has been used experimentally in research studies with patients with psychotic major depression. In these studies, mifepristone was well tolerated, and no serious side effects or medication-related problems were reported.

15.0 Data Safety Monitoring Board

The Indiana University Adult Psychiatry Data Safety Monitoring Board (DSMB) will be responsible for data and safety monitoring. DSMB is responsible for reviewing study procedures, adverse events, safety mailings (if applicable), enrollment, active subjects, and ongoing conduct of the research. The DSMB members can ask questions and make comments and/or recommendations. The IRB is notified of significant findings by way of the DSMB meeting minutes at the time of continuing review. An updated DSMB member list will be provided at the time of IRB continuing review or upon request.

Due to the small sample size and single site design of this protocol, there is not sufficient justification for conducting interim analyses to examine trends.

Data on the number of subjects enrolled and the number of adverse events will be reviewed by the DSMB at least **quarterly** and more frequently if needed. The resultant report will be issued to the IRB at the time of continuing review or more frequently by request.

Any unanticipated events will be immediately directed to the principal investigator who will follow the Indiana University IRB reporting procedures.

16.0 Statistical Considerations

Continuous variables will be summarized by treatment groups using descriptive statistics including mean, standard deviation, and range. Categorical variables will be summarized using frequency counts and percentages. Baseline clinical and demographic data will be compared between the two treatment groups to assess the effectiveness of the randomization. Dichotomous and ordinal variables will be examined using chi-square tests and continuous measures with Student's t-tests. Appropriate exact and non-parametric methods will be used as needed. The primary goal of this study will be to estimate the effect size for the treatment on the BPDSI total score. This will be done at each time point, as we are also interested in how the effect is sustained after active drug treatment is discontinued. We also will graph the trajectory of each subject over time. Supportive analyses will be based on the linear mixed effects model with a random subject effect for BPDSI with time, treatment and time by treatment interaction as covariates. The model parameters will be estimated using SAS MIXED procedure and the p-values for the comparisons of the differential treatment effects and 95% confidence interval for the treatment effect will be reported. The time by treatment interaction will be assessed to examine whether the active drug effect was changing over time. Secondary outcomes and serum cortisol levels will be examined similarly. Graphs, Pearson or Spearman correlations, and linear mixed models will be used to examine the relationship between serum cortisol levels and outcome measures. Due to the small sample size, covariates (type of abuse, age of abuse onset, abuse duration, diagnosis of MDD, diagnosis of PTSD) will be examined graphically. Safety analyses of this study will include summarized counts and rates per treatment group of the incidence of the adverse events. Incidences of selected adverse events from the two treatment arms will be compared using the Fisher's exact test on an exploratory basis.

Sample Size Justification: This is a pilot study designed to estimate effect sizes for a future randomized trial. It is recommended that a minimum of 12 subjects per group be used for this purpose based on estimating the precision of the meant treatment effect and variance (13).

17.0 Privacy/Confidentiality Issues

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the principal investigator and research staff. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the principal investigator and research staff. Any screening information obtained from potential research subjects who subsequently do not participate in the research study will be destroyed.

18.0 Record Retention

Paper copies of medical records and source documentation will be kept for seven years after the study is closed with the IRB. One year after study closure, the documents will be shipped to the Indiana University Department of Psychiatry long-term storage facility until destruction.

19.0 Bibliography

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ATTACHMENT 1
Study Procedures Table

Visit	**1**	**2**	**3**	**4**	**5**	**6**
Day		0	4	7	14	28
Visit Window (days since last visit)		14-30	4	3	7	14
Informed Consent	X					
SCID I & II	X					
Medical History	X					
Demographics	X					
Physical Exam	X					
Vitals	X	X	X	X	X	X
Verification of Preg Prevention	X	X	X	X	X	X
ECG[a]	X	X	X	X	X[b]	X[b]
CGI-S/I	X[c]	X[c]		X	X	X
BPRS		X		X	X	X
BPDSI (90-day)	X					
BPDSI (7-day)		X		X	X	X
BPD Checklist		X		X	X	X
ITEC[d]	X					
SCL-90-R		X		X	X	X
IPII		X				X
CBC	X					
CMP	X	X		X	X	X
Serum Preg test (beta HCG)	X					
Blood Cortisol Level		X		X[e]	X[e]	X[e]
Biobank Blood Sample		X				X
Pharmacokinetics[f]				X		
Urine Pregnancy Test	X	X	X	X	X	X
Adverse Events			X	X	X	X
Concomitant Medication		X	X	X	X	X
Medication Dispensation		X				
Medication Accountability			X[g]	X		

a Triplicate tracings to be collected at least 1 minute apart

b Subsequent ECG tracings will be collected at V5 and V6 at the discreption of the principal investigator

c CGI-I will not be completed at Visits 1 or 2 as there is no "improvement" score at baseline.

d Clinician may use abbreviated version of form, at principal investigator's discretion

e Subsequent blood collection to occur at the exact time of day as the baseline value (+/- 30 minutes)

f Pharmacokinetic analysis will be completed based off of time of study drug from previous day.

g Study medication will be reviewed during this visit for compliance purposes. Study medication will not be returned or dispensed at this visit

NOTE: Visit split procedures will not be considered protocol deviations

V 02.03.15

ATTACHMENT 2
Concomitant Medication Table

Prohibited	
Class	Name/*Subclass*
Antibiotics	*Anti-Malarials*
	Anti-Mycoplasmics
	Azole Antifungals
	Chloramphenicol
	Fluoroquinolones
	Pentamidine
	Macrolides
Anesthetics/	Buprenorphine
Analgesics	Fentanyl
	Methadone
	Sevoflurane
Anticonvulsant/	*Barbiturates*
Mood-Stabilizers	Carbemazepine
	Oxcarbazepine
	Phenytoin
Antidepressants/	*Benzodiazepines*[a] (clonazepam is PERMITTED)
Anxiolytics/	Buspirone[h] (Caution. Uses of $\leq$ 30mg total daily dose is PERMITTED)
Hypnotics	Bupropion
	Citalopram[b] (Caution. Uses of doses $\leq$ 20mg daily dose is PERMITTED)--See additional notes
	Escitalopram[c] (Caution. Uses of doses $\leq$ 10mg daily dose is PERMITTED)----See additional notes
	Eszopiclone[i] (Caution. Uses of $\leq$ 1mg total daily dose is PERMITTED)
	Nefazodone
	Zaleplon[j] (Caution. Uses of $\leq$ 5mg total daily dose is PERMITTED)
	Zolpidem[j] (Caution. Uses of $\leq$ 5mg total daily dose is PERMITTED)
Antipsychotics/	Aprepitant
Antiemetics	Asenapine
	Chlorpromazine
	Droperidol
	Haloperidol
	Iloperidone
	Ondansetron
	Paliperidone[k]
	Pimozide
	Quetiapine[k]
	Thioridazine
	Ziprasidone[k]

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Concomitant Medication Table (Cont.)

Cardiovascular/	Amiodarone
Dyslipidemics	*Calcium Channel Blockers*
	Clopidogrel
	Digoxin
	Disopyramide
	Dofetilide
	Dronederone
	Flecainide
	Ibutilide
	Quinidine
	Sotalol
	Statins[d]
	Warfarin
Hematologics/	Anegrelide
Oncologics	Arsenic Trioxide
	Chemotherapeutics
Herbals/Foods	Ginko Biloba
	Grapefruit
	Milk Thistle
	Star Fruit
	St. John's Wort
	Tonic Water
	Valerian
Others	Beta agonist (short acting)[e]
	Beta agonist (long acting)
	Corticosteroids[f,g]
	Conivaptan
	Cyclosporine
	Dihydroergotamine
	Efavirenz
	Ergotamine
	Mifepristone (Mifeprex, Korlym, RU486)
	Nevirapine
	Phosphodiesterase Inhibitors
	Pioglitazone
	Protease Inhibitors
	Replaglinide
	Sirolimus
	Tacrolimus
	Troglitazone

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Concomitant Medication Table (Cont.)

a. Except for clonazepam, use of which is PERMITTED.
b. Caution. Uses of doses ≤ 20mg daily dose is PERMITTED. Uses of doses > 20mg daily dose, but < 40mg daily dose is CAUTIONED due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is within normal limits per a cardiologist overread of ECG tracings. Uses of doses > 40mg daily dose is EXCLUSIONARY
c. Caution. Uses of doses ≤ 10mg is PERMITTED. Uses of doses > 10mg, but < 20mg is CAUTIONED due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is within normal limits per a cardiologist overread of ECG tracings. Uses of doses > 20mg is EXCLUSIONARY.
d. Except for rosuvastatin, pitavastatin, & pravastatin.
e. Beta agonists (short acting) for PRN use are permitted. Subjects are to REFRAIN from use while on the study medication and for one week after discontinuation of study medication as using these medications as they may cause a temporary change in electrolyte levels which could increase the chance of a dangerous heart rhythm abnormality. If subjects require the use of these medications during this time period, they should be under the direct observation of a physician (e.g. on an inpatient unit, in an emergency room, or at a physician's office) for additional monitoring.
f. Topical and inhaled corticosteriods are OK.
g. Exclusionary: 4 weeks prior to randomization and on study medication
h. Caution. Uses of ≤ 30mg total daily dose is PERMITTED. CAUTIONED due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is within normal limits per a cardiologist overread of ECG tracings. Uses of doses > 30mg daily dose is EXCLUSIONARY.
i. Caution. Uses of ≤ 1mg total daily dose is PERMITTED. CAUTIONED due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is within normal limits per a cardiologist overread of ECG tracings. Uses of doses > 1mg daily dose is EXCLUSIONARY.
j. Caution. Uses of ≤ 5mg total daily dose is PERMITTED. CAUTIONED due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is within normal limits per a cardiologist overread of ECG tracings. Uses of doses > 5mg daily dose is EXCLUSIONARY.
k. Caution. Due to the possibility of QTc prolongation. The subject may only be included in the study if QTc is < 430msec cardiologist overread of ECG tracings and magnesium and potassium are within normal limits or determined not clinically significant by a principal invesigator or medical designee.