Gabapentin for Bipolar & Cannabis Use Disorders: Relation to Brain GABA/Glutamate

NCT03334721

10/25/2017

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Protocol

10/16/17

Specific Aims

Bipolar disorder (BD) is the Axis I condition most strongly associated with cannabis use disorder (CUD); there is a six-fold increase in the prevalence of CUD in individuals with BD relative to the general population. Individuals with co-occurring CUD and BD (CUD+BD) have substantially worse clinical outcomes than those with either BD or CUD alone. Response to mood stabilizing medications appears to be poor, yet little is known about optimal treatment for CUD+BD, as there have been no randomized medication trials for CUD+BD to date. Convergent evidence supports dysregulated brain γ-Aminobutyric acid (GABA)/glutamate homeostasis as a candidate target for pharmacological intervention in CUD+BD. Preclinical and clinical studies have demonstrated that CUD and BD are each associated with prefrontal GABA and glutamate disturbances and that impulsivity, a core neurobehavioral feature of both CUD and BD and a key Research Domain Criteria (RDoC) construct, is causally related to GABAergic/glutamatergic functioning. Gabapentin has been consistently shown in preclinical research to modulate GABA and glutamate transmission. In human Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) studies, both acute and chronic gabapentin dosing have been shown to increase brain GABA levels, however, few studies have investigated gabapentin effects on glutamate levels. We propose that gabapentin may impact clinical outcomes in CUD+BD individuals both directly and indirectly through their impact on impulsivity.

The proposed 2-week, double-blind, crossover, proof of concept study will focus on GABA, while exploring glutamate, disturbances in CUD+BD and will evaluate: a) whether gabapentin, a medication that has been demonstrated to increase cortical GABA concentrations in healthy controls and individuals with epilepsy, may similarly act to increase dorsal anterior cingulate and basal ganglia GABA levels in individuals with CUD+BD, and b) whether increased dorsal anterior cingulate and basal ganglia GABA levels will be associated with increased functional brain activity to response inhibition (“go no-go”) cues (a well-studied neurobehavioral probe of impulsivity) as well as decreased functional brain activity to cannabis cues. Effects of gabapentin on cannabis use, mood symptoms (including anxiety and sleep), and impulsivity will be explored.

Hypothesis 1: Gabapentin will increase dorsal anterior cingulate and basal ganglia GABA concentrations, relative to placebo, in individuals with CUD+BD.

Hypothesis 2: Gabapentin-related increases in dorsal anterior cingulate and basal ganglia GABA concentrations will be associated with, a) increased brain activity to response inhibition (“no-go”) cues relative to response activation (“go”) cues and b) decreased functional brain activity to visual cannabis cues relative to neutral cues.

Exploratory Hypotheses: 1) Given the lack of data on gabapentin and glutamate, associations between gabapentin and dorsal anterior cingulate/basal ganglia glutamate concentrations, and between gabapentin-related changes in glutamate concentrations and functional brain activity to response inhibition and cannabis cues, will be explored. 2) Associations between gabapentin-related changes in dorsal anterior cingulate/basal ganglia GABA and glutamate concentrations and cannabis use, mood symptoms (including anxiety and sleep), and impulsivity over the course of the study will be explored.

In summary, the proposed 2-week, double-blind, crossover, proof of concept study aims to measure and manipulate core neurochemical (i.e., dysregulated brain GABA/glutamate homeostasis) and neurobehavioral (i.e., elevated impulsivity) dysfunctions characteristic of individuals with CUD and BD, using a medication that has been shown to increase cortical GABA (i.e., gabapentin) levels in past research, and to evaluate medication-related changes in response inhibition (go no-go) and cannabis cue reactivity functional Magnetic Resonance Imaging tasks, as well as cannabis use, mood symptoms (including anxiety and sleep), and impulsivity in individuals with CUD+BD. Positive results may support investigation of gabapentin for the treatment of CUD+BD in large-scale, randomized clinical trials. The proposed study may also provide successful demonstration of a neurobehavioral, multimodal neuroimaging platform for evaluating the potential promise of other GABAergic drugs for CUD and/or BD, as well as other conditions marked by GABA/glutamate dysfunction.

A. SIGNIFICANCE

A.1. Overview. There is a six-fold increase in the prevalence of cannabis use disorder (CUD) in individuals with bipolar disorder (BD) relative to the general population[1]. Co-occurring CUD and BD (CUD+BD) is associated with more frequent mood cycling[1], poorer quality of life[1], disability[2] and psychosis[3] relative to BD alone, even in individuals receiving state-of-the-art pharmacotherapy for BD[4]. Response to mood stabilizing medications is poor[5, 6], yet little is known about optimal treatment as there have been no controlled trials (RCTs) for CUD+BD. Evidence supports disrupted brain γ-Aminobutyric acid (GABA)/glutamate (GLU) homeostasis as a target for pharmacological intervention in CUD+BD. Gabapentin may work through this mechanism to treat CUD+BD.

A.2. GABA and GLU Dysregulation in CUD and BD. GABA and GLU, the main inhibitory and excitatory neurotransmitters (NTs) in mammals, respectively, are principally involved in the coordination of cortical activity, synaptic plasticity and modulation of other NT systems[7, 8]. The extant literature supports a role for dysregulated GABA and GLU transmission in CUD and BD. Preclinical research suggests that the reorganization of reward circuitry in substance use disorders (SUD) to preferentially respond to drug cues, manifesting clinically as drug craving and seeking, may be due to substance-induced neuroplasticity mediated by GLU and GABA[9, 10]. Cannabinoids have been shown to decrease $GABA_A$-mediated inhibitory, and NMDA/AMPA-mediated excitatory, transmission[11] via activation of cannabinoid type-1 (CB_1) receptors located on presynaptic GABA/GLU neurons[12] that are particularly abundant in cortex and basal ganglia (BG)[13]. BD studies have demonstrated links between genes responsible for coding ionotropic GLU receptor subunits, BD[14], and lithium response[15], as well as reduced levels of cerebrospinal fluid (CSF) and plasma GABA[16, 17] and differences in GABA receptor genes[18-20]. Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) studies provide the opportunity to better understand these issues in humans. ^{1}H-MRS studies in CUD individuals have demonstrated decreased GLU and GABA levels in anterior cingulate cortex (ACC)[21, 22] as well as decreased GLU in right BG (rBG)[23, 24]. ^{1}H-MRS studies of BD have demonstrated elevated prefrontal GLU across mood states[25-31], and state-of-the-art (MEGA-PRESS) GABA studies have found abnormal ACC and occipital cortex GABA levels as well[32-34]. Impulsivity, the tendency to respond without forethought, has been hypothesized as a "critical link" between SUD and BD[35]; it is a core neurobehavioral feature of both CUD[36] and BD[37] and is causally related to GABA/GLU function[38, 39]. Preclinical studies have shown that injections of NMDA receptor antagonists[39], as well as the $GABA_A$ receptor agonist muscimol[38], are associated with impulsive behavior. ^{1}H-MRS studies have demonstrated a positive association between anterior cingulate cortex (ACC) glutamate and impulsivity[40] and a negative association between dorsolateral PFC[41] and ACC[40] GABA and impulsivity across clinical populations. Finally, fMRI investigations, which have primarily focused on the response inhibition facet of impulsivity, have consistently demonstrated differences in prefrontal activation to inhibition cues in both BD[42] and CUD[43] individuals relative to controls. In sum, studies have found that CUD and BD are each associated with prefrontal GABA/GLU disturbances and that impulsivity, a core neurobehavioral feature of both CUD and BD, is causally related to GABA/GLU function. Medications that normalize brain GABA/GLU may, therefore, impact clinical outcomes in CUD and BD both directly and indirectly through their impact on impulsivity (a key Research Domain Criteria [RDoC] construct).

A.3. Gabapentin for Restoring GABA/GLU Homeostasis. ^{1}H-MRS studies have consistently demonstrated that three GABAergic medications increase brain GABA levels: gabapentin, topiramate, and vigabatrin[44]. Gabapentin has been shown to significantly raise occipital GABA levels 1-6 hours following a single dose (900-1200mg) in healthy controls[45, 46] and epileptics[47]. Long-term gabapentin dosing has also been shown to significantly increase occipital GABA in controls (2400mg/day)[46] and epileptics (1200-3600mg/day)[47, 48]. Most studies reported average increases of 25-50%, with individuals with lower baseline levels showing the largest increases in GABA with gabapentin[45, 47]. Whereas topiramate and vigabatrin are associated with significant side effects including cognitive dysfunction[49], particularly during rapid dose-titration, gabapentin is well-tolerated and safe. Although preclinical studies have consistently found decreased GLU release with gabapentin administration, the only ^{1}H-MRS gabapentin study in humans to measure GLU found that acute gabapentin (900mg) did not change GLU levels[45]; multiple doses may be necessary to elicit a GLU response. Preclinical studies have also demonstrated that pregabalin, a GABA-analogue with high structural similarity to gabapentin, blocks motor signs and anxiety behaviors associated with cannabis withdrawal[50]. Basic human studies have found that both gabapentin and the $GABA_B$-selective agonist, baclofen, shift the discriminative-stimulus effects of Δ^9-THC leftward/upward, suggesting that these agents may improve CUD outcomes by producing cannabis-like interoceptive effects[51, 52]. Preclinical studies of gabapentin that have focused on other substances of abuse (e.g., ethanol, cocaine) have demonstrated decreased, a) self-administration[53, 54], b) stressor/cue-induced reinstatement[53], c) expression/development of stimulant sensitization[55, 56], d) drug-induced place preference[56], and e) anxiogenic effects of withdrawal[54]. Effects of gabapentin in these studies appear to be mediated, in part, by normalization of GABAergic transmission in central amygdala[54] and elevation of α2/δ-1 subunit of voltage-

gated calcium channels[56]. Research has also demonstrated that the efficacy of gabapentin may be moderated by variation in $GABA_A$ receptor subunits α 1 and 3; as such, genetic investigation for the present study will focus on associated single nucleotide polymorphisms (e.g., rs10068980, rs1112122, rs1157122, rs4828696, rs511310, rs6883877, rs6892782, aggregated in https://www.pharmgkb.org/chemical/PA449720#tabview=tab1&subtab=31) along with variation in genes that code for NMDA and AMPA receptors, as these receptors appear to be impacted by gabapentin treatment (Rose and Kam, 2002); interestingly, many of these same SNPs have been shown to differentiate individuals with and without mood disorders (Brambilla et al., 2003). A recent RCT demonstrated reduced cannabis use and withdrawal in adults with CUD who were treated with gabapentin (1200mg/day)[57]; no other medications have demonstrated efficacy for reducing cannabis use in adults with CUD[58]. Despite a long history of positive reports from open-label studies in BD[59], two RCTs, with a number of methodological concerns (e.g., unstructured clinical interview used to diagnose BD, inappropriate handling of missing data), failed to support an effect of gabapentin on reducing acute mood symptoms in treatment-refractory manic outpatients[60] or an admixed sample of medication-free inpatients with BD or unipolar depression[61]. Conversely, results from an additional RCT in euthymic BD supported gabapentin as a prophylactic agent[62]. Important to the proposed study, gabapentin has demonstrated efficacy in treating symptoms that are disproportionately present and impairing in individuals with CUD+BD relative to those with CUD or BD alone (e.g., anxiety, impulsivity, insomnia)[59, 63]. Since impulsivity is a core feature of both CUD and BD, it might be particularly targeted. In sum, gabapentin has been shown to restore GABA/GLU homeostasis, with treatment studies demonstrating efficacy in reducing cannabis use/craving, anxiety, impulsivity, and insomnia in individuals with CUD or BD. CUD+BD may be a unique population where gabapentin may have synergistic benefits given the magnifying effects of CUD on GABA/GLU function.

A.4. Conclusion. The proposed 2-week, double-blind, crossover study aims to normalize the dysregulated brain GABA/GLU homeostasis characteristic of individuals with CUD and BD using gabapentin, a medication shown to restore GABA/GLU homeostasis, and to evaluate medication-related changes in brain activation to cannabis and response inhibition (impulsivity) cues, as well as mood and cannabis use, in individuals with CUD+BD.

B. INNOVATION

1) No RCTs for CUD+BD have been conducted to date. Positive results from the proposed study may not only provide support for the investigation of gabapentin for the treatment of CUD+BD in large RCTs, but may also indicate the utility of other interventions affecting GABA/GLU transmission, while simultaneously substantiating a tailored imaging platform for testing the promise of such interventions, in individuals with CUD and/or BD.

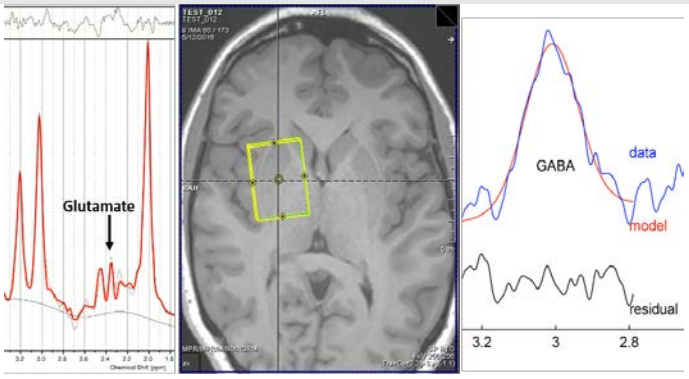
2) Although convergent evidence supports GABA/GLU disturbances in CUD and BD, no ^{1}H-MRS studies have investigated these disturbances in individuals with co-occurring CUD and BD. The proposed study will be the first to investigate whether altering GABA/GLU balance in individuals with CUD+BD results in changes in neurobehavioral and clinical variables.

C. RESEARCH PLAN

C.1. Preliminary Studies

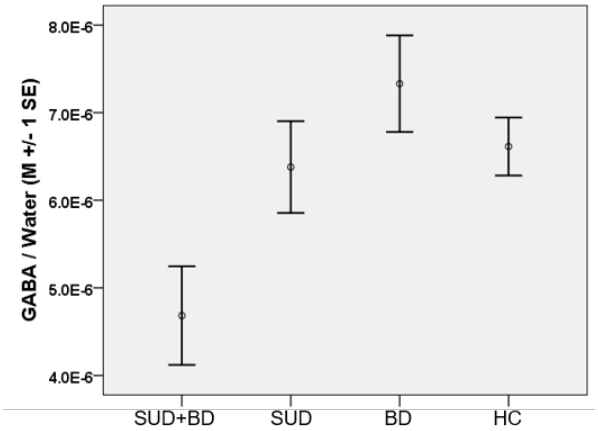
C.1.a. Recruitment Experience. Drs. Prisciandaro and Tolliver (Co-I) have years of experience of successfully recruiting/retaining research participants with SUD+BD (AA020842, AA017666)[64]. Although these studies have primarily focused on AUD+BD, 40-50% of participants were also diagnosed with CUD. Furthermore, additional subjects with CUD+BD, but not AUD, could have been available for the proposed study. Finally, Dr. McRae-Clark (Co-I) has an extensive track record of recruiting individuals with CUD to federally funded trials[65].

Figure 1. Sample rBG voxel (center), fitted PRESS GLU spectrum (left), fitted MEGA-PRESS GABA spectrum (right).



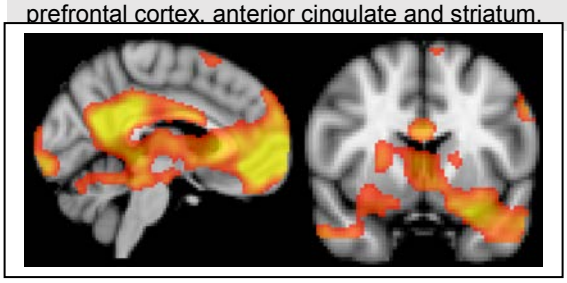
C.1.b. ^{1}H-MRS Experience. Drs. Prisciandaro has acquired dorsal ACC (dACC) ^{1}H-MRS data from >200 subjects to date[66], including >100 scans (using the same sequences proposed herein) for an RCT of gabapentin in AUD (AA022364, PI: Anton). Data quality has been excellent. We conducted 5 scans of rBG in controls using the proposed ^{1}H-MRS protocol. Data quality was uniformly good (water linewidth <12 Hz). See Figure 1, above.

Figure 2. *Abnormally low dACC GABA in SUD+BD.*



C.1.b. Preliminary data from Dr. Prisciandaro's K23 study demonstrated uniquely low levels of dACC GABA in individuals with SUD+BD (n=20) vs. SUD (n=20) or BD (n=19) alone or healthy controls (n=19) (Fig 2, left). A similar statistically significant interaction was found for dACC glutamate if the sample was restricted to individuals who drank/used drugs within 2 w of MRI. (All SUD+BD participants met AUD criteria within 6 m of MRI and 80% of SUD+BD met lifetime Drug Use Disorder criteria; 40% of SUD+BD met past-year CUD criteria).

Figure 3. Robust activation was elicited from cannabis, vs. neutral, stimuli in heavy cannabis users in reward regions including the medial prefrontal cortex, anterior cingulate and striatum.



C.1.c. Functional Magnetic Resonance Imaging (fMRI) Exerience. Dr. Squeglia (Co-I) developed a Cannabis Cue Reactivity (CCR) fMRI task consisting of cannabis and neutral images that is useful for probing the neurobehavioral effects of gabapentin: 1) cue reactivity appears to be GABA/GLU mediated[9, 10], 2) cue reactivity/craving are important clinical targets[67], and 3) reward sensitivity (congruent with the RDoC construct, Approach Motivation), arguably best characterized by CCR in CUD+BD[68], is a core neurobehavioral deficit in both CUD[69, 70] and BD[71-73]. Preliminary data, from 41 heavy (M=2x/day) cannabis users (46% women, M age=18.7 ±0.51) demonstrated significant activation to cannabis vs. neutral cues (cluster-corrected $z > 2.3$, $p < 0.05$) in regions involved in reward processing, including bilateral medial prefrontal, striatum, dACC, subcallosal, precuneus, and posterior cingulate cortex (Figure 3). As noted in C.2.e (Procedures), the proposed response inhibition ("go no-go") fMRI task, included to better target dACC activation) has been featured in a number of PI-authored publications[74, 75].

C.2. Research Design and Methods. The proposed 2-week, double-blind crossover study will evaluate: a) the effects of gabapentin on basal dACC and rBG GABA and GLU concentrations and b) the effects of changes in GABA and GLU levels on brain activity to cannabis and response inhibition (impulsivity) cues. The relationship between changes in GABA and GLU levels, brain activation to cannabis/response inhibition cues, and clinical symptoms (e.g., cannabis use, impulsivity, mood and anxiety) will be explored. Participants will complete two, 1-week experimental conditions (gabapentin, placebo) in a randomized order. Each condition will consist of a visit for assessment and dispensing of medication (Day 1), titration to maximum dose (1200mg/day) (Days 1-5), MRI (Day 5), and medication washout (Days 5-7). Spacing of appointments cited throughout the protocol refers to ideal conditions which may be minimally deviated from if needed (e.g., +/- 1 day between medication and MRI visits, 1 week between conditions). See Figure 4 below for a full study design schematic.

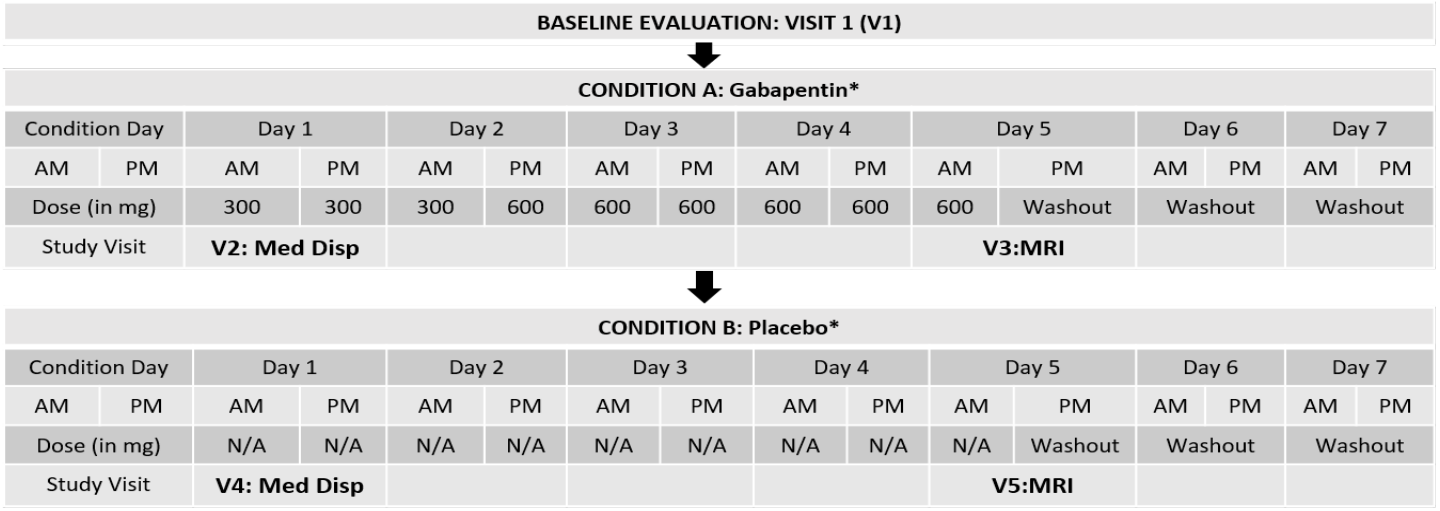


Figure 4. Study design schematic. *Condition order will be randomized between participants. Med Disp = Medication Dispensing.

C.2.a. Strategies to Ensure a Robust/Unbiased Approach: Explicit inclusion/exclusion criteria; randomization of condition order/examination of order effects; placebo control; double blinding; compliance monitoring; use of validated MRI, laboratory, and interview/self-report measures/methods; explicit hypotheses and planned statistical analyses; power estimates; planned handling of attrition and missing data; and careful consideration of potential confounds. Methodology is reported in a detailed and fully transparent manner to support replication.

C.2.b. Participants. Twenty-three healthy, clinically stable men and women age 18-65 with both CUD and BD (or schizoaffective disorder, bipolar type) will be enrolled. Inclusion/exclusion criteria are fully listed below.

C.2.c. Concomitant Medications. Participants will be required to be taking a stable regimen of ≥1 FDA-approved mood stabilizing medications for BD; restricting the study to medication-naïve individuals would represent a safety hazard and would severely limit recruitment[76]. To minimize the impact of medications on results: 1) individuals taking benzodiazepines > 3x/week will be excluded; positive benzodiazepine UDS at baseline, potentially reflecting residual excretion of benzodiazepines with long half-lives (e.g., valium), will be further investigated by the PA and/or study physician. Individuals taking atypical antipsychotics will not be excluded, as ^{1}H-MRS studies have failed to demonstrate associations between antipsychotic medication load and brain GLU/GABA levels[77-79], and 2) participants with medication additions, discontinuations, or major dose changes ≤ 2 weeks prior to testing will be excluded[80]. Concomitant medications will be assessed at each visit and considered as covariates/moderators in all analyses.

C.2.d. Recruitment. Recruitment will occur via clinical referral and low-cost advertising (e.g., Craigslist, WeSearchTogether.com, ResearchMatch.com) over an 18-month period to reach an enrollment target of 1.25 CUD+BD participants/month. This project will use ResearchMatch.org, a web-based recruitment tool, to assist with enrollment for this study. An e-mail message that, per ResearchMatch's request, excludes researchers direct contact information will be sent to potential study volunteers through this tool. ResearchMatch's standard notification language that will be received by all ResearchMatch volunteers who may be a match for a given study. WeSearchTogether.com will also be utilized in this study which is a web-based recruitment tool for individuals that are interested in research related to mood. Referral will prioritize 4 sites:

- The Center for Drug and Alcohol Programs (CDAP) is an inpatient/outpatient SUD treatment facility within the MUSC Institute of Psychiatry (IOP). Dr. Tolliver (Co-I) is an attending psychiatrist in the CDAP inpatient unit (4N; 0.8 FTE). 40% of participants from our past SUD+BD studies were referred from CDAP.
- The IOP general inpatient unit (3N) has a capacity of 25-30 and regularly refers BD patients to the PI.
- The Ralph H. Johnson VA Medical Center is a tertiary care facility with inpatient, outpatient, and residential SUD services from where 20% of Dr. Tolliver's BD clinical trials subjects were recruited.
- The Charleston Center is an SUD treatment facility located 1 block from MUSC that screens >2,500 patients/year and provides inpatient, outpatient, and residential treatment. Dr. McRae-Clark (Co-I) has a long history of collaboration with Charleston Center through her work with NIDA's Clinical Trials Network.

In addition to these methods of recruitment, a chart review will be conducted for research purposes. Potentially eligible patients will be identified. The potentially eligible patients in the investigators' practice will be informed about the study as the investigator feels is appropriate. Then potential patients who have agreed to be contacted for future research by logging their MUSC Research Permissions preferences in MyChart will be contacted via telephone and invited to participate. All other patients will be contacted through their providers to be informed of

the study if the provider feels it is appropriate. Concerning the RHJVAMC, we will seek separate approval through the VAMC to post and distribute VA-approved study fliers.

Table 1. Schedule of events by study visit					
Study Visit	Visit 1 Evaluation	Visit 2 Med Disp	Visit 3 MRI	Visit 4 Med Disp	Visit 5 MRI
Clinician and PA					
Informed Consent* / HIPAA* / BrAC contract*	X				
SCID-5 (Mood/Substance)*	X				
TLFB* (90 day at V1)	X	X	X	X	X
YMRS* / MADRS* / C-SSRS*	X	X	X	X	X
BDRS / BR		X	X		X
Observe Dose (note time)		X	X	X	X
H&P* / Metal Screen*	X				
AEs / Vitals		X	X	X	X
Self-Report					
Demographics / Family history	X				
BDI* / PSQI* / BAI*	X				
BIS-11 / SPSRQ / AUDIT / ASRS / WHODAS / DSM-5 PID5/PQ	X				
BDI PW / PSQI PW / BAI PW (PW=Past Week)		X	X		X
FTND / ASRM / MCQ / CWS	X	X	X		X
Actiwatch Data Download			X	X	X
Urge to use MJ [1-10] (PRE/POST MRI)					X
Computer Tasks					
STOP-IT	X		X		X
Delay Disc	X				
GoGoNoGo Practice			X		
CNL Labs					
CMP* / CBC* / DNA*	X				
%dCDT		X			
Gabapentin level			X		X
EtG		X	X		X
Riboflavin		X	X		X
Cannabinoids/Creatinine Levels		X	X	X	X
In-House Labs					
Collect urine specimen* / UDS*	X	X	X	X	X
Breathalyzer*	X	X	X	X	X
Pregnancy Test*	X		X		X
Saliva drug screen		X	X		X

Note: "*" Indicates assessments that must be done at Visit 1. Non-starred assessments at Visit 1 can be completed at Visit 2 if needed.

C.2.e. Procedures. See Table 1.

Eligibility and Medical / Psychiatric Assessment (Visit 1). Following brief screening over the phone or at a referral site, potential participants will be scheduled for formal screening at an Addiction Sciences Division research clinic. They will read and sign an IRB-approved informed consent (IC) document and will then be assessed for eligibility using the Structured Clinical Interview for DSM-V[81]. Trait impulsivity will be assessed via the Barratt Impulsiveness Scale (BIS-11)[82]. Past 90 day drug/alcohol use will be assessed with the Timeline Followback (TLFB)[83]. Cannabis use will be recorded in times used/day as well as quantity (e.g., grams, number of joints) to standardize for different types of use. Participants will be asked to quantify cannabis use by weighing out amounts of an inert surrogate and reporting on that amount's potency through dollar value estimates. Recent methods of use will then be quantified using this system (bowls, bongs, blunts, ingestion)[84]. Cannabis craving will be measured using the 12-item, Marijuana Craving Questionnaire (MCQ)[85]. Past 24-hour withdrawal symptoms will be assessed using the Cannabis Withdrawal Scale (CWS)[86]. Mood symptoms will be assessed using the clinician-administered Young Mania Rating Scale (YMRS)[87] and Montgomery-Asberg Depression Rating Scale (MADRS)[88, 89], supplemented with items from the Bech-Rafaelsen Mania Rating Scale (Bech et al., 1978) and Bipolar Depression Rating Scale (Berk et al., 2007), along with the self-report Beck Depression Inventory-II (BDI-II)[89], Beck Anxiety Inventory (BAI)[90], and Altman Self Rating Mania Scale (ASRM; Altman et al., 1997). Sleep will be assessed using the Pittsburgh Sleep Quality Index (PSQI)[91]. Personality pathology (Personality Inventory for DSM-5; PID-5; Suzuki et al., 2015), ADHD symptoms (Adult ADHD Self-Report Scale; ASRS; Kessler et al., 2005), functional impairment (WHO Disability Assessment Scale; WHODAS; WHO, 2010), Sensitivity to Punishment and Sensitivity to Reward (SPSRQ; Torrubia et al., 2001), alcohol use severity (AUDIT; Saunders et al., 1993), and family psychiatric history (Sachs et al., 2003) will also be assessed. A breathalyzer/intoxication policy will be provided to each participant to indicate steps taken by clinical staff if the participant's reading is over 0.08. Given that GABA/GLU dysfunction in BD is evident across mood states[25-31], participants reporting mood symptoms will not be excluded in order to maximize feasibility and generalizability to clinical populations. Safety assessments, including the Columbia Suicide Severity Rating Scale (C-SSRS)[92], will be conducted at each visit to assess for symptomatology requiring medication adjustment or hospitalization (see Human Subjects for full safety plan). MRI safety will also be assessed. Potential participants will undergo a full medical history and physical exam and will provide samples for blood chemistries (General Health Panel [CMP], Complete Blood Count [CBC]) and genetic testing. Qiagen DNA extraction kits are used to extract DNA from whole blood by a dedicated genetic technician in Dr. Anton's lab, tested for DNA purity, and used in Taqman PCR analysis with specific probes and primers purchased from Life Science Technologies using a Step One analyzer (Applied Biosystems). Dr. Anton's KO5 funding allowed him to become proficient in this type of analysis and he has genotyped hundreds of samples with various SNP's and VNTR's including the glutamate and GABA genes of interest (see background section). Qualitative drug screens will be performed using the Discover 12 Panel Cup®, an in vitro diagnostic test for the detection of drug/drug metabolite in urine. Urine will also be tested for Ethyl Glucuronide (EtG) to evaluate recent alcohol drinking. Participants will provide a saliva sample to test for recent cannabis use using SalivaConfirm® (Confirm Biosciences, Inc). Semi-quantitative urine cannabinoid screens (detection cut-off=20.00 ng/ml) will be performed, and normalized to creatinine[93], using the Architech® system from Abbott Laboratories. Female participants will take pregnancy tests. Finally, eligible participants will complete two brief (<10m) computer tasks to measure delay discounting (Green et al., 1994) and stop signal reaction time (STOPIT; Verbruggen et al., 2008).

Inclusion Criteria: 1) Subjects must meet DSM-5 criteria for current CUD and provide a positive urine cannabinoid screen at baseline. They must additionally self-report cannabis use within the past 30 days and report using more days than not in the month preceding abstinence. 2) Subjects must meet DSM-5 criteria for bipolar disorder (or schizoaffective disorder, bipolar type) and must be prescribed daily use of ≥1 mood stabilizing medication (i.e., lithium, atypical antipsychotic, divalproex sodium / valproate, carbamazepine, lamotrigine). 3) Women of childbearing potential must utilize effective birth control.

Exclusion Criteria: 1) History of significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological disease. 2) History of psychotic disorder (e.g., Schizophrenia). 3) Current suicidal or homicidal ideation. 4.) Subjects meeting DSM-5 criteria for moderate/severe SUD (other than nicotine or cannabis) within the past month. 5) Concomitant use of benzodiazepines (>3x/week), or electroconvulsive therapy in the past month. 6.) History of clinically significant brain injury. 7.) Presence of non-MRI safe materials or significant claustrophobia. 8.) Use of medications hazardous if taken with gabapentin. 9.) History of allergic reaction to gabapentin. 10.) Plasma creatinine levels > 2x the normal range. 11.) Clinically significant mania (YMRS > 25) or severe depression (MADRS > 35), to ensure safety and decrease between-subjects variability.

Medication Dispensing (Visits 2, 4). Participants will complete any assessments not required for

inclusion/exclusion determination and not completed at Visit 1 at Visit 2. At Visit 2, participants will be asked to wear an actigraphy watch (Actiwatch Spectrum Plus, Philips Respironics) on their non-dominant wrist for the remainder of the study. They will be instructed on its use (e.g., not to take it off when showering) and asked to keep a brief actigraph log (e.g., sleep and wake times) delivered daily via text/e-mail using REDCap. On day 1 of each condition, mood symptoms (YMRS, MADRS, C-SSRS) and alcohol/drug consumption (TLFB, UDS) will be assessed. Medications will be packaged and dispensed by the MUSC Investigational Drug Service (IDS). IDS will oversee blinding procedures for the study and maintain treatment assignment records. Medication will be over-encapsulated with riboflavin (25mg/capsule), for urinary detection by fluorescence spectroscopy at each MRI, with each capsule containing either 300mg of gabapentin or matching placebo dispensed in blister packs. At each Dispensing visit, participants will take their first dose in front of study staff to ensure compliance. They will receive detailed instructions regarding the dosing schedule for days 1-5 of the condition (See Figure 4). Gabapentin has an elimination half-life of 6-7 hours[94]. Participants should reach steady state concentrations of the maximal dose (1200mg) well before the MRI visit[95]. Twice daily dosing will be used to maximize compliance. The proposed titration schedule is consistent with our experience with gabapentin for AUD[96-98], gabapentin studies in CUD[57], and our clinical experience with dual diagnosis patients. Unused medications will be returned for pill counts. Gabapentin blood levels will be obtained for all participants, in house, using a validated immunoassay[99]. Medication adherence will be evaluated as a covariate. Due to flexibility in scheduling (+/- 1 day for the MRI visit), extra medication will be provided for each participant and labeled as such to ensure participants have the correct number of doses.

MRI (Visits 3, 5). MRI visits will take place on day 5 of each condition. Participants will be asked to abstain from drugs/alcohol ≥12 hours prior to MRI. They will take their final dose of medication in front of study staff, 1 h prior to MRI, to ensure compliance. Participants who smoke will be allowed to have their last cigarette immediately prior to their final medication dose. Mood symptoms (YMRS, MADRS, C-SSRS, BDI, BAI, ASRM, PSQI), alcohol/drug/tobacco consumption (TLFB, UDS, FTND, EtG, Saliva), cannabis withdrawal (CWS), and cravings (MCQ) will be assessed. Participants will provide a urine and blood sample to test for gabapentin levels, riboflavin, liver function, and alcohol/drug consumption. Following structural and ^{1}H-MRS scanning, participants will complete the CCR and go no-go fMRI tasks in counterbalanced order (see below) with the Natural Rewards Task at the end. fMRI tasks will be conducted while acquiring BOLD weighted transverse scans using a gradient-echo, echo-planar imaging (EPI) sequence: TR/TE=2200/35 ms; flip angle=90°; field of view=220x220 mm; voxel size=3.00x3.00 mm; 37 contiguous 3-mm-thick slices. Total scan time is approximately 75 m in a Siemens 3.0T Prisma (32-channel head coil). Participants will discontinue study medication following each MRI and will remain off study medication on days 6-7 of the condition. Given that the last gabapentin dose will be taken in the morning of day 5, this will provide approximately 11 half-lives of elimination prior to the start of the next condition. Crossover studies employing up to 3x the proposed dose of gabapentin have demonstrated an absence of carryover effects on clinical outcomes given the same[100] or fewer[101] days of washout as proposed herein. Potential carryover effects will be carefully examined using the proposed analytic design. Outside of the scanner, participants will complete the STOP-IT task. Within approximately 72 hours of day 7 of the final study condition, participants will be contacted by clinically-trained study staff to discuss adverse events, alcohol and drug consumption, and mood stability since discontinuing study medication.

^{1}H-MRS Acquisition. A structural scan will be taken for ^{1}H-MRS voxel placement and tissue segmentation (256 sagittal slices; 1mm thick/50% gap). dACC and rBG contain different concentrations of GABA[102] and form an important fronto-striatal reward circuit[103]. We will acquire data from both regions to evaluate whether gabapentin effects, as well as associations between GABA and cannabis/response inhibition cue-reactivity, are region specific. The dACC voxel will be placed on midsagittal T1-weighted images, posterior to the genu of the corpus callosum, with the ventral edge aligned with the dorsal edge of the callosum[104]. An rBG voxel will be placed on an axial T1-weighted slice about 1 cm above the genu, between the Sylvian fissure and the lateral ventricles including corpus striatum[105]. Each voxel will be 2.5x2.5x3 cm^3 to ensure adequate signal to noise. Following placement of 6 saturation bands at least 1 cm away from the voxel faces and auto-shimming via FASTESTMAP, single-voxel water-suppressed ^{1}H-MRS spectra will be acquired using a MEGA-PRESS sequence (TR=2000ms; TE=68ms; number of averages=300) with symmetric editing pulse frequencies (1.9 ppm and 1.5 ppm) for macromolecule suppression[106] and a PRESS sequence maximally sensitive to GLU (TR=2000ms; TE=40ms; number of averages=128)[107]. Unsuppressed water spectra will be acquired for each sequence.

Cannabis Cue Reactivity. During the CCR fMRI task, participants are shown pseudorandomly interspersed cannabis (cannabis plant, paraphernalia) and neutral (e.g., pine cone, trumpet) images, visual control (blurred) images, and a fixation cross. The cannabis stimuli were matched by color, hue, and complexity. Stimuli are presented in six 120 s epochs, each consisting of four blocks of an image type. Participants rate their “urge to

use marijuana" after each block, 0 ("none") to 4 ("severe"), using a handpad. See Figure 3 for preliminary data.
Response Inhibition (Impulsivity). The "go no-go," response inhibition, fMRI task consists of 20 blocks, lasting 26.25 s each; 10 go no-go blocks alternate with 10 fixation blocks, in which a cross is presented for the duration of the block. During go no-go blocks, participants are presented with 21 letters, one at a time, for 250 ms each, followed by 1 s interstimulus intervals (black screen). They are instructed to press a button on their handpad as soon as they see a letter other than "X," but to withhold response if they see the letter "X," which is presented 20% of the time. Presentation order of letters is randomized to remove confounding effects due to the overlap of hemodynamic responses. This task was featured in several publications authored by the PI[74, 75].
Natural Rewards Task. The natural rewards paradigm, recently developed by Drs. Mellick, Prisciandaro, and McTeague, contains pictures of social rewards (romance, family, children and babies), food rewards, and nonsocial and household object control images; all of which were selected from the International Affective Picture System (IAPS; Lang et al., 2005) and matched in color and hue. Chosen pictures were carefully selected based on prior fMRI research with natural rewards and alcohol cues (e.g., Garavan et al., 2000; Tomasi et al., 2015; Ihssen et al., 2010). These studies were most informative to the selection of food and household object control images. As social rewards have yet to be examined as they are in this task, a bottom-up approach was taken in picture selection. Best practices as outlined in the IAPS technical manual were adhered to when forming each picture category (Lang et al., 1997). First, the entire IAPS catalog, was reviewed and candidate pictures were identified based on content. Pictures were then excluded for composition, color, contrast, hue, and cropping. Those which may be interpreted as ambiguous by participants were also excluded. Next, normative valence (unpleasant to pleasant) and intensity (calm to excited) ratings, provided by IAPS developers, were reviewed with the goal of selecting social and food pictures high in valence and intensity, and nonsocial and household object control images of neutral valence and low intensity. Specific to the nonsocial control category, pictures depicting people looking towards the viewer were excluded to avoid activation in regions associated with facial recognition (e.g., fusiform gyrus; Haxby et al., 2000).

C.2.f. Statistical Considerations

Sample Size Determination. Data from an ongoing investigation of gabapentin for AUD (n=21), where participants are scanned prior to, and 2 weeks following, initiation of gabapentin treatment or placebo, were used to inform power calculations for the proposed study; as the study remains blinded, estimates of variability and correlation between scan 1 and 2 GABA concentrations were taken from the combined sample. An estimate of anticipated dropout was derived from Dr. Tolliver's trial of lamotrigine in AUD+BD, where 20% of participants dropped out by week 3. According to these estimates, with 18 completers (23 enrolled with 20% dropout), the proposed study would have >80% power to detect a ≥25% increase in GABA given a ≥0.60 correlation of GABA estimates across scans (observed r =0.72). Gabapentin studies have found 25-50% increases in GABA[45, 46, 48].

^{1}H-MRS/fMRI Processing. MEGA-PRESS (GABA) data will be analyzed using the Gannet MATLAB toolbox[108] and PRESS (GLU) data using LCModel 6.3[109]. Metabolites with fitting uncertainties <20% will be retained. Within-voxel tissue fractions of gray and white matter and CSF will be calculated based on automated segmentation in Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Cognitive Neurology)[110]. Metabolite concentrations will be normalized to the unsuppressed water signal and corrected for within-voxel CSF fraction. fMRI analysis will be completed in SPM12. Standard fMRI preprocessing including realignment, normalization, and smoothing will be performed. Preprocessed data will be analyzed within a general linear model mixed effects framework. For the CCR task, the main contrast of interest will be the cannabis vs. neutral images contrast. For the go no-go task, the main contrast of interest will be the no-go vs. go trial contrast. Following 1st-level analysis, subject-specific spatially-normalized contrast maps will be entered into 2nd-level, random-effects analyses. Condition parameter maps will be thresholded at $p<0.05$, corrected for multiple comparisons.

Data Analysis. Generalized linear mixed effects models will be employed to assess the effect of gabapentin on dACC and rBG GABA levels (Hypothesis 1). As detailed above, whole-brain random-effects analyses will be conducted to assess the direct effect of gabapentin, as well as the direct effect of gabapentin-induced changes in GABA, on brain activation to cannabis and response inhibition (impulsivity) cues (Hypothesis 2). These analyses will be supplemented with a region of interest approach (extracting % signal change from participants' ^{1}H-MRS voxels) using the MarsBaR SPM toolbox. Primary models for Hypotheses 1 and 2 will contain the main effect of treatment, period (scan 1 v. scan 2), and sequence (gabapentin 1st v. placebo 1st) to ensure the crossover design and washout were successful. All models will be re-estimated with GLU levels entered in place of GABA (Exploratory Hypothesis 1). To synthesize hypotheses 1-2, mediation models will be estimated in which metabolite levels are posited as mediators of the association between medication treatment and brain activity to

cannabis and response inhibition cues[111]. We will employ previously successful methods to minimize attrition, but mixed effects models can be used to provide valid estimates assuming data are missing at random[112].

Exploratory/covariate analyses. 1) Mood and substance use: It is likely that mood and substance use will vary within individuals, across visits. We will examine associations between mood (YMRS, MADRS), substance use (TLFB, UDS, EtG, Saliva), and GABA and GLU levels, and will evaluate mood and substance use variables as covariates in all analyses. Potential medication-related changes in anxiety (BAI), sleep (PSQI), and impulsivity will also be explored (Exploratory Hypothesis 2). 2) Age, sex, smoking status, AUD, anxiety disorder, concomitant medications. Age, sex, and smoking status have been associated with GABA and GLU levels in the extant literature[113-115]. Co-occurring anxiety disorders and AUD are very common in individuals with BD[116, 117] and have been associated with GABA/GLU dysregulation[104, 118, 119]. Participants with anxiety and AUD will not be excluded to enhance feasibility/clinical generalization. Given the within-subjects design of the study, between-subjects variables are not potential confounders; nonetheless, we will consider these variables as moderators in all analyses. Potential indications of sex differences will be considered in future, larger studies.

C.2.g. Potential Limitations. 1) Previous studies that have demonstrated gabapentin-induced increases in brain GABA have been conducted in controls and epileptics. Whether these findings will generalize to CUD+BD is unknown. 2) Mood and substance use are potential confounders of condition comparisons as they can change over the course of the study in a given individual. Their impact on study outcomes will be carefully examined and they will be evaluated as potential covariates in all models. 3) A potential challenge to completing the study will be recruiting/retaining a sufficient number of CUD+BD participants. If recruitment goals are consistently not met, the study team will meet to discuss strategies for meeting goals without compromising the integrity of the study.

C.2.h. Future Directions. Positive results may support investigation of gabapentin for the treatment of CUD+BD in large RCTs. The proposed study may also provide successful demonstration of a multimodal imaging platform for evaluating the promise of other GABA/GLU drugs for CUD and/or BD. This study will also add to the literature on associations between GABA/GLU and RDoC constructs central to CUD/BD (impulsivity and cue reactivity).

C.2.i. Timeline. Purchasing, setup, and regulatory approval will be completed within the first 3 months of Yr 01. 11-12 participants will be recruited/year. Analysis and manuscript submission will begin in the 2nd half of Yr 02.

Protection of Human Subjects

1. **Risk to the Subjects**

a. Human Subject Involvement and Characteristics. A total of 23 individuals in stable medical condition will be enrolled in the study. Women and minorities will be recruited for this study. Children and adolescents under the age of 18 will not be enrolled.

Inclusion Criteria:

1. Age 18-65
2. Meet DSM-5 criteria for current CUD, provide a positive urine cannabinoid screen at baseline, self-report cannabis use within the past 30 days and using cannabis more days than not in the month preceding abstinence.
3. Meet DSM-5 criteria for bipolar I or II disorder (BD) or schizoaffective disorder, bipolar type.
4. Able to provide informed consent and read, understand, and accurately complete assessment instruments
5. Willing to commit to medication treatment and follow-up assessments
6. Prescribed daily use of at least one mood stabilizing medication (i.e., lithium, atypical antipsychotic agents, divalproex sodium / valproate, lamotrigine, carbamazepine)

Exclusion Criteria:

1. A primary psychiatric diagnosis other than BD (e.g., Schizophrenia)
2. Meet DSM-5 criteria for moderate or severe substance use disorder (other than nicotine or cannabis) within the past month.
3. Any uncontrolled neurologic condition (e.g., epilepsy) that could confound the results of the study
4. Any history of clinically significant brain injury
5. Any history of mental retardation, dementia, or electroconvulsive therapy in the past month
6. Any uncontrolled medical condition that may adversely affect the conduct of the study or jeopardize the safety of the subject
7. Hepatocellular disease as indicated by plasma levels of liver transaminases (aspartate transaminase, alanine transaminase) greater than 3 times the normal range
8. Reduction in creatinine clearance greater than 2 times the normal range
9. Concomitant use of medications that could interfere with glutamatergic/GABAergic transmission (e.g., benzodiazepines > 3x/week, ceftriaxone, riluzole, memantine, ketamine, topiramate, vigabatrin), due to potential confounding effects
10. Azelastine, orphenadrine, oxomemazine, paraldehyde, and thalidomide are contraindicated in patients taking gabapentin; as such, individuals taking these medications will be excluded
11. Women of childbearing potential who are pregnant, lactating, or refuse adequate forms of contraception
12. Current suicidal or homicidal risk
13. Baseline scores greater than 35 on the Montgomery-Asberg Depression Rating Scale or greater than 25 on the Young Mania Rating Scale
14. Has taken gabapentin in the last 2-weeks or experienced adverse effects/allergic reaction (e.g., angioedema) from it at any time
15. Significant claustrophobia and/or past negative experiences with MRI
16. Presence of non-MRI safe materials in the body (e.g., ferrous metal implants, pacemaker)

b. Source of Materials. Data collected from participants will include breathalyzer readings, urine drug screens, urine biomarkers (e.g., riboflavin, ethyl glucuronide), blood chemistries, structural, functional, and neurochemical MRI brain images, and interviews and self-reports regarding substance use, psychiatric diagnoses, concomitant medications, and adverse events. To ensure confidentiality, all participant data will be number-coded, and only the investigators will have access to the master list of codes. A federal Certificate of Confidentiality, protecting participants against disclosure of sensitive information (e.g., drug use), will be obtained for the study.

c. Compensation. To maximize participant retention, contingency management will be applied to participant compensation such that participants will be compensated significantly more for each subsequent MRI visit they

attend (i.e., scan 1 = $100, scan 2 = $150), and participants will be given an additional $50 bonus for completing both MRI visits without rescheduling and for returning their actigraphy watch. Participants will be compensated $10/hour (rounded to the nearest half-hour) during the diagnostic visit if screened out during this time. Participants will be compensation $50 for completing the full initial psychiatric and medical evaluation appointment. Finally, participants will be compensated $30 for each additional non-MRI appointment (i.e., 2 total). Following the initial appointment, participants will be compensated weekly, at the end of each MRI session; $50 of each week's compensation will be contingent on them returning their actigraphy watch to the appointment. Total compensation will thus be $410 per participant. In our experience, this level of compensation is fair for the time commitment required without unduly coercing participants to enroll in the study despite potential concerns.

d. Potential Risks

1. Medication side effects. Gabapentin is generally well-tolerated, with sedation and dizziness being the most commonly reported side effects[96, 97]. Although the FDA has issued a class warning for antiepileptic drugs and suicidal thoughts and behavior, available data do not support an association between gabapentin, specifically, and increased suicidal ideation or behavior in individuals with BD or other psychiatric populations[97, 98]. The proposed study will minimize potential medication-related risks by implementing low starting doses and titration of study medications and will carefully monitor potential medication-related risks via biweekly scheduled visits and assessment of adverse events (including assessment of suicidal ideation and behavior at each and every study visit). The study physician will determine if the participant should be discontinued from the medication due to adverse drug reactions and will treat clinically as needed. Any confirmed incidence of serious adverse events that are deemed probably or definitely due to the study medication will result in immediate discontinuation of the study medication and follow-up assessments will be conducted until resolution. Subjects will be referred for treatment as necessary.
2. Drug interactions. Azelastine, orphenadrine, oxomemazine, paraldehyde, and thalidomide are contraindicated in patients taking gabapentin; as such, individuals taking these medications will be excluded. As noted earlier, participants will be required to be taking a stable pre-existing regimen of at least one FDA-approved mood stabilizing medication treatment for BD. There are no known serious drug interactions with gabapentin and mood-stabilizing medications.
3. MRI-related risks. Individuals with non-MRI-safe medical implants or ferrous objects would be at risk for injury, if such individuals were allowed to enter the MRI scanner. Several precautions will be taken to ensure that individuals with ferrous implants or objects are not allowed to enter the MRI scanner. First, all potential participants will meet with a study physician to discuss any possible history of ferrous implants or other MRI-unsafe objects. Participants with any suspected history of ferrous implants or exposure to shrapnel will be excluded from the study. Second, participants who are deemed MRI-safe by the study physician will be screened for metal objects at the Center for Biomedical Imaging (CBI) using a handheld metal detector and a second metal detector built into the threshold of the doorway to the scanner. Participants who screen positive for metal will be asked to remove all metal objects from their person and will be rescreened. If participants continue to screen positive for metal after removing all metal objects from their person, they will be excluded from the study. Although not dangerous, participants who are claustrophobic could experience significant discomfort in the MRI scanner. As such, all participants will be assessed in terms of claustrophobia as well as past experience with MRI. Additionally, all participants will be entered into a "mock scanner" at the CBI human imaging center, which features the same dimensions of the real MRI scanner but without any of the internal machinery. Participants who report claustrophobia, past negative experience with MRI, or signification discomfort in the mock scanner will be excluded from participation. These procedures have been successfully used by our staff in previous and ongoing research studies of similar participant populations. For those participants allowed to participate in the MRI study, if abnormalities in collected brain images are found, participants will immediately be referred to an appropriate clinical care provider.
4. Cue-elicited cannabis craving. It is possible that the cannabis cue exposure functional MRI paradigm could induce cannabis craving. Participants will be asked to rate their craving from one to ten both immediately preceding and following the neuroimaging protocol. Post-scan craving ratings twenty percent above baseline will require study approved clinicians to come and speak with the patient before they are discharged. Should any craving fail to subside within 3-4 hours, participants will be provided with counseling by clinicians; appropriate referrals will be made as needed. These procedures have been successfully used by our staff in previous and ongoing research studies of similar participant populations.
5. Cannabis consumption and withdrawal. Subjects will not be required to establish abstinence at any time during the study, however, they may voluntarily attempt abstinence during the course of the study. Participants who voluntarily attempt abstinence may experience cannabis withdrawal symptoms. Study

participants will be monitored for cannabis withdrawal symptoms. Conversely, participants may continue to consume cannabis. The risks of continued cannabis use may include but are not limited to psychiatric morbidity, increased risk of traumatic injury, and other medical consequences. If in the PI's opinion a participant has significant worsening of cannabis use problems or consumption of cannabis as a result of participating in the study, the subject will be withdrawn from the study and appropriately referred.

6. Mood destabilization. Exacerbation of depressive or manic symptoms during the course of the study is a risk for all subjects regardless of treatment condition. We will minimize this risk by assessing mood symptoms, including suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS), at each and every study visit. Participants experiencing sufficient deterioration of mood stability to result in clinically significant impairment in functional capacity will be appropriately referred. Any subject exhibiting mood destabilization that is sufficient to pose an imminent danger to self or others will be hospitalized immediately and removed from the study.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent. Recruitment will occur by clinical referral, response to advertisements and flyers, and chart review. The principal investigator, the study coordinator, co-investigators with completed masters-or-higher-level clinical training will obtain informed consent. At the screening visit, potential participants will be provided a copy of the IRB-approved consent document to review. After providing the participant with time to read the consent, the principal investigator, the study coordinator, co-investigators with completed masters-or-higher-level clinical training will review the consent document page by page with the participant and answer any questions. Only then will the participant be asked to sign the consent document. Participants will be given a copy of the signed consent document. The entire informed consent process will be documented in the research progress notes. The signed, original consent document will be maintained in the participant source record with a copy of the consent binder located at the Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina.

b. Safety Assessments. At every visit, clinically-trained study staff will evaluate subjects' manic and/or depressive symptoms, including suicidal ideation. Mood symptoms will also be quantified using standardized instruments including MADRS, YMRS, BDI-II, and BAI. Adverse events will be assessed at every study visit.

c. Protection Against Risk.

Psychiatric Risks. The investigative team has a great deal of experience working with the study population and have the resources to make appropriate referrals as needed. Psychiatric symptoms will be assessed on a biweekly basis by standardized assessments and by clinical interview. Participants scoring >4 on the suicide item (item 4) of the MADRS; endorsing items 4 ("Have you had these [suicidal] thoughts and some intention of acting on them?"), 5 ("Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?"), or 6 ("Have you done anything, started to do anything, or prepared to do anything to end your life?") on the C-SSRS, or otherwise exhibiting potentially life-threatening decompensation in mood or other psychiatric symptoms at any study visit will be removed from the study and referred for outpatient or inpatient treatment as necessary.

Medical Risks. Gabapentin is excreted by a renal route. A blood chemistry panel will be performed and reviewed by the study physician prior to beginning the study medication. Participants with clinically significant renal, or hepatic (transaminases elevated > 3 times normal), insufficiency will not be eligible to participate in the study. Subjects will be referred for treatment as necessary.

MRI Risks. The investigative team has a great deal of experience with human MRI research and Dr. Prisciandaro is a core faculty member of the CBI at MUSC. MRI safety and comfort will be assessed at baseline and at each MRI visit. Participants with non-MRI-safe medical implants or ferrous objects will be excluded from participation as will individuals evidencing significant discomfort with MRI.

Pregnancy. Gabapentin is rated as a Category C medication in terms of pregnancy. Because there are no adequate controlled studies of gabapentin in pregnant women, it is unknown whether the drug can cause fetal harm or affect reproductive capacity in humans. Therefore, women of childbearing potential must agree to pregnancy testing and use of adequate contraception in order to be eligible to participate in the study. Females will be given a urinary pregnancy test at the screening visit and weekly thereafter. Any female participant who becomes pregnant during the study will be discontinued from the study medication and removed from study participation. For all included females of childbearing potential, current forms of birth control and date of last menstruation will be assessed at each study visit.

Confidentiality. Records with identifying information (e.g., consent documents) will be stored in a locked file. All other non-MRI participant data will be collected via direct data capture (REDCap); MRI data will be automatically transferred to Linux-based servers managed by CBI. Both MRI and non-MRI data will be stored in restricted access directories on password-protected, encrypted servers managed by CBI and the Department of Psychiatry and Behavioral Sciences at MUSC. Participants will be given an ID number for all MRI and non-MRI data files. The master list of codes will be accessible only to the investigators, and will be stored in a locked office. As noted above, a federal Certificate of Confidentiality, protecting participants against disclosure of sensitive information (e.g., drug use), will be obtained prior to study initiation.

Emergencies. All study participants will be instructed how to access the 24-hour on-call system available at the Medical University of South Carolina. In the event that a participant experiences an adverse event after hours, s/he will be instructed to access the 24-hour on-call service. If it is determined that the participant needs immediate help, the participant may be advised to immediately go to the emergency room. In that event, proper medical treatment will be administered, per ER procedures. Dr. Prisciandaro and Dr. Tolliver will be available by pager/cell as necessary. The Investigational Drug Service (IDS) will be available 24 hours/day, 7 days/week for emergency identification of treatment group assignment and unblinding as necessary.

Substance Abuse Treatment. Subjects may receive additional non-pharmacologic substance abuse treatment during study participation. Attendance at group-based recovery activities (e.g., Narcotics Anonymous) will be encouraged and monitored.

3. Potential Benefits of the Proposed Research to the Subjects and Others

Benefits to the subjects include medical and psychiatric assessments provided at no cost. Subjects may benefit by reduction of cannabis consumption as an effect of active treatment or through nonspecific effects of study participation (increased awareness of cannabis consumption, frequent interactions with study personnel, etc.), although this is not guaranteed for any given subject. Other individuals with comorbid CUD and BD are likely to benefit by the knowledge gained from the study as it may help guide future treatments.

4. Importance of the Knowledge to Be Gained

There is a six-fold increase in the prevalence of CUD in individuals with BD relative to the general population; this common comorbidity is associated with substantially elevated negative outcomes, including treatment resistance. Treatment research for co-occurring CUD and BD is extremely limited, with no randomized trials for CUD+BD conducted to date. The proposed study will evaluate the ability of a medication (i.e., gabapentin) that has been shown to increase cortical GABA levels in past research to manipulate a neurochemical dysfunction characteristic of individuals with CUD+BD (i.e., dysregulated brain GABA/glutamate homeostasis). Positive results may support investigation of gabapentin for the treatment of CUD+BD in large-scale, randomized clinical trials. Furthermore, the proposed study may provide successful demonstration of a neurobehavioral, multimodal neuroimaging platform for evaluating the potential promise of GABAergic drugs for CUD and/or BD, as well as other conditions marked by GABA/glutamate dysfunction. The proposed investigation's minimal risks are reasonable in relation to the importance of the knowledge to be gained from the investigation.

5. Clinicaltrials.gov Requirements

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

Data and Safety Monitoring Plan

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan".

1) Summary of the Protocol.

This application proposes to investigate the effects of gabapentin on brain GABA and glutamate concentrations, a neurobehavioral measure of cannabis cue-reactivity, and mood and cannabis use in individuals with co-occurring cannabis use disorder and bipolar disorder. The primary outcomes of interest are brain GABA and glutamate levels and a neurobehavioral measures of cannabis cue-reactivity. Inclusion/exclusion criteria are outlined in Protection of Human Subjects. Power calculations and sample sizes are detailed in the Sample Size Determination section of the Research Strategy.

2) Trial Management.

The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC). The target population is described above in the inclusion/exclusion criteria.

3) Data Management and Analysis.

Non-MRI data will be collected via direct data capture (REDCap) on tablet devices and stored on MUSC centralized secured, backed-up servers. MRI data will be automatically transferred to Linux-based servers managed by the Center for Biomedical Imaging (CBI). The data analysis plan is outlined in the Data Analysis section of the Research Strategy.

4) Quality Assurance.

Quarterly data audits will be conducted. Confidentiality protections are outlined above.

5) Regulatory Issues.

Potential conflicts of interest will be reported using the upcoming NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented, and reported in accordance with protocol and Institutional Review Board (IRB) reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research assistant will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research assistant will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Any significant actions taken by the local IRB and protocol changes will be relayed to NIDA.

6) Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect OR
- Requires intervention to prevent one of the above outcomes.

7) Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research staff will notify the MUSC IRB within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting. A report will also be sent to the NIH program officer assigned to the project.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIDA Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the MUSC IRB online as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

8) Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Study procedures will follow the FDA’s Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Dr. Prisciandaro.

9) Trial Efficacy.

An interim analysis is not planned at this time.

10) DSM Plan Administration.

Drs. Prisciandaro, Tolliver, McRae-Clark, Anton, and Squeglia will be responsible for monitoring the study, and will participate in weekly study meetings. A DSM report will be filed with the IRB and NIDA on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report outcomes at the end of the trial.

11) DSM Board.

A Data Safety and Monitoring Board will be formed to monitor both the rate and severity of adverse events. This panel will include 3 clinicians with expertise in cannabis use and mood disorders and a statistician.

12) Risk Benefit Ratio.

The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality and adverse events to gabapentin or MRI. As discussed above, our research

team will attempt to minimize these risks. Knowledge gained by the proposed study would help fill an important void in development of a potential treatment for co-occurring cannabis use disorder and bipolar disorder.

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