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Results from a randomized, double-blind, placebo-controlled, crossover, multimodal-MRI pilot study of gabapentin for co-occurring bipolar and cannabis use disorders

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Abstract

Disrupted brain gamma-Aminobutyric acid (GABA)/glutamate homeostasis is a promising target for pharmacological intervention in co-occurring bipolar disorder (BD) and cannabis use disorder (CUD). Gabapentin is a safe and well-tolerated medication, FDA-approved to treat other neurological diseases, that restores GABA/glutamate homeostasis, with treatment studies supporting efficacy in treating CUD, as well as anxiety and sleep disorders that are common to both BD and CUD. The present manuscript represents the primary report of a randomized, double-blind, placebo-controlled, crossover (1-week/condition), multimodal-MRI (proton-MR spectroscopy, functional MRI) pilot study of gabapentin (1200mg/day) in BD+CUD (n=22). Primary analyses revealed that, A) gabapentin was well-tolerated, adherence and retention were high, B) gabapentin increased dorsal anterior cingulate cortex (dACC) and right basal ganglia (rBG) glutamate levels, and C) gabapentin increased activation to visual cannabis cues in the posterior midcingulate cortex (pMCC, a region involved in response inhibition to rewarding stimuli). Exploratory evaluation of clinical outcomes further found that, in participants taking gabapentin versus placebo: 1) elevations of dACC GABA levels were associated with lower manic/mixed and depressive symptoms and 2) elevations of rBG glutamate levels and pMCC activation to cannabis cues were associated with lower cannabis use. Though promising, the findings from this study should be interpreted with caution due to observed randomization order effects on dACC glutamate levels, and identification of statistical moderators that differed by randomization order (i.e., cigarette-smoking status on rBG glutamate levels and pMCC cue-activation). Nonetheless, they provide the necessary foundation for a more robustly-designed (urn-randomized, parallel-group) future study of adjuvant gabapentin for BD+CUD.

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AUTHORSHIP

JJP was responsible for the study concept and design. LMS contributed the Cannabis Cue Reactivity fMRI Task. WM, BKT, LA, and SH contributed to data acquisition. JJP and WM performed the data analysis. JJP drafted the manuscript. LMS, BKT, and WM provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

INTRODUCTION

There is an 8-fold increase in the prevalence of cannabis use disorder (CUD) in individuals with bipolar disorder (BD)[1] relative to the general population[2]. Co-occurring BD and CUD (BD+CUD; relative to BD alone) is associated with more frequent mood cycling, mixed manic and depressive symptoms, poorer quality of life, elevated risk of cigarette-smoking and psychosis, and greater rates of disability, hospitalization, and suicide[1,3–5]. Treatment response to mood-stabilizing medications FDA-approved for BD is poor in individuals with BD+CUD[6,7]. Overall, little is known about optimal treatment of BD+CUD, as there have been no randomized controlled trials (RCTs) in this population to date.

Convergent evidence supports dysfunctional brain gamma-Aminobutyric acid (GABA) and glutamate neurotransmission as promising targets for pharmacological intervention in CUD and BD[8,9]. The reorganization of reward circuitry in CUD to preferentially respond to drug cues, manifesting clinically as drug craving/seeking, is due to drug-induced neuroplasticity mediated by glutamate and GABA[10,11]. Delta-9-tetrahydrocannabinol (Δ9-THC, the psychoactive component of cannabis) activates pre-synaptic cannabinoid type-1 (CB_1) receptors that are densely distributed in frontostriatal brain regions, facilitating release (and reducing astrocytic uptake) of glutamate resulting in accumulated extracellular glutamate, and inhibiting release of GABA resulting in disinhibition of mesolimbic dopaminergic cells critical to the development of CUD[8]. Repeated Δ9-THC administration induces down-regulation and internalization of CB_1 and glutamate receptors, and suppresses activity of glutamic-acid decarboxylase and glutamine synthetase, resulting in reduced synaptic glutamate and GABA transmission[12].

Consistent with preclinical findings, Δ9-THC significantly increased glutamate levels, measured using proton magnetic resonance spectroscopy (^{1}H-MRS), in the left caudate head (part of the striatum/basal ganglia) of healthy volunteers[13]. Chronic cannabis use and CUD have been, in turn, associated with, decreased anterior cingulate cortex (ACC, located in the medial-frontal lobe)[14,15] and right basal ganglia (rBG)[16,17] glutamate levels, decreased ACC GABA levels[15], and heightened activation to cannabis cues in many of the same frontostriatal brain regions, which underlie reward, attention, motivation, and goal-directed behavior (e.g., ACC/medial-prefrontal cortex [mPFC], striatum/basal ganglia)[18,19].

In contrast, ^{1}H-MRS studies of BD have consistently demonstrated *elevated* glutamate levels across mood states and brain regions[9]. Investigations of GABA using the MEGA-PRESS acquisition technique have consistently found abnormal ACC and occipital cortex GABA concentrations in BD[20–22], although the direction of disturbance has not been consistent. Though there have been no published studies of brain glutamate and GABA levels in BD+CUD, CUD was associated with reduced mPFC glutamate levels in individuals with early psychosis (subsuming BD and schizoaffective disorder, bipolar type)[23]. We similarly found that individuals with co-occurring BD and alcohol use disorder (AUD; with/without co-occurring CUD) had significantly lower dorsal ACC (dACC) levels of both GABA and glutamate relative to individuals with BD alone, AUD alone, or healthy volunteers, and that lower dACC GABA levels were associated with elevated alcohol craving and impulsivity[24]. Together, these studies suggest that although BD is associated with *elevated* glutamate

levels[9], BD appears to act like a "multiplier" to the impact of Substance Use Disorder (SUD) on *lowering* glutamate levels, reducing them well below levels associated with SUD alone[23,24].

Gabapentin, a safe and well-tolerated medication that is FDA-approved to treat post-herpetic neuralgia, partial seizures, and restless-leg syndrome, holds promise as an adjuvant medication for normalizing brain GABA and glutamate transmission in individuals with BD+CUD. Gabapentin is known to modulate GABA and glutamate transmission via selective blockade of presynaptic voltage-gated calcium channels that contain the α2δ−1 subunit[25]. More recently, additional mechanisms have been identified, including activation of potassium channels[26], increased expression of postsynaptic δ-subunit-containing $GABA_A$ receptors[27], and reduced spontaneous synaptic-glutamate release dependent on α2δ−1-linked *N*-methyl-D-aspartate (NMDA) receptors[28]. In ^{1}H-MRS studies, gabapentin significantly increased occipital GABA levels 1–6 hours following a single dose (900–1200mg) in healthy volunteer[29,30] and patients with epilepsy[31]. Longer-term gabapentin dosing (i.e., ≥ 2-week) has also been shown to significantly increase occipital GABA, in a dose-dependent manner, in healthy volunteers (2400mg/day)[30] and patients with epilepsy (1200–3600mg/day)[31,32]; though, ≥ 1-week of daily (*M* = 1,600mg/day) gabapentin was not associated with altered cortical GABA levels in a convenience sample of alcohol-dependent individuals during short-term abstincence[33].

In neurobehavioral studies, gabapentin reduced cannabis use and withdrawal symptoms in cannabis-dependent adults[34], distinguishing it as one of few promising medications for CUD warranting further research[35]. Gabapentin substitutes for Δ9-THC-discriminative stimuli in cannabis users, suggesting that it may reduce cannabis use by producing interoceptive effects that may replace those of Δ9-THC[36]. Furthermore, the gabapentinoid, pregabalin, blocked motor signs and anxiety behaviors associated with cannabis withdrawal in mice[37]. Animal studies focused on other SUDs found decreased self-administration[38,39], reinstatement[38], and conditioned place preference[40] with gabapentin, mediated, in part, by normalization of GABAergic transmission in central amygdala and elevation of α2δ−1 subunit of voltage-gated calcium channels[39,40]. Although RCTs in treatment-refractory BD failed to support gabapentin for resolving acute mood episodes, one RCT demonstrated a prophylactic effect of gabapentin in BD[41], and a long history of positive reports from open-label studies support the use of gabapentin for BD patients suffering from anxiety and sleep disturbance[42].

The present study represents the primary report of an NIH/NIDA-funded (R21DA043917), randomized, double-blind, placebo-controlled, crossover, multimodal-MRI pilot study of gabapentin (1200mg/day) as an adjunctive medication for BD+CUD that evaluated the following hypotheses: 1) gabapentin will increase dACC and rBG GABA and glutamate levels (^{1}H-MRS), and 2) gabapentin will decrease brain activity to visual cannabis cues (functional MRI, fMRI). Associations of changes in GABA and glutamate levels with cannabis use and mood symptoms were also explored.

SUBJECTS AND METHODS

Participants.

Twenty-two individuals, ages 18–65, who met DSM-5 criteria for BD-I or -II and *current* (within the past 3-months) moderate-to-severe CUD[43], and who provided a positive urine cannabinoid screen at baseline, were recruited from clinical settings and advertisements and enrolled into the study across an 18-month period (see Table 1 for participant characteristics by Randomization Order [RO] and Supplemental Figure 1 for CONSORT diagram). Three participants diagnosed with Bipolar-I Disorder (n=2 in RO#1, n=1 in RO#2) were given a provisional diagnosis of Schizoaffective Disorder, Bipolar Type, following retrospective reports of hallucinations/delusions in the absence of a clear Mood Episode. Participants were required to document daily use of ≥1 FDA-approved mood-stabilizing medication for BD (lithium, lamotrigine, divalproex sodium, carbamazepine, 2nd-generation antipsychotic), as restricting the study to medication-naïve individuals would have represented a safety hazard, severely limited recruitment[44], and would have been inconsistent with the purpose of the study (to evaluate gabapentin as an *adjuvant* medication). To minimize the impact of medications on results, participants with additions, discontinuations, or dose changes of >20%, <2-weeks prior to testing were excluded (Swann, 2009). Other exclusion criteria included history of significant medical illness, traumatic brain injury, or non-affective psychotic disorder (e.g., Schizophrenia); severe mood disturbance (Montgomery-Asberg Depression Rating Scale [MADRS][45] >35 and/or Young Mania Rating Scale [YMRS][46] >25) or suicidal/homicidal ideation; meeting DSM-5 criteria for moderate-to-severe SUD other than cannabis or tobacco within 60-days of evaluation; opioid or benzodiazepine use, as indicated by positive urine drug screen and/or self-report; pregnancy; and presence of non-MRI-safe implants or claustrophobia.

A target sample size (≥18 study-completers) was chosen to provide ≥80% power to detect a ≥25% increase in GABA, as past gabapentin studies reported GABA increases of 25–50%. Our most recent evaluation of the test-retest reliability of dACC GABA levels in 10 healthy volunteers, acquired via MEGA-PRESS with echo times of 68ms or 80ms, produced within-subject coefficient of variation (CV_{ws}) estimates of approximately 8% (i.e., irrespective of echo time) (unpublished data), which is in-line with[47] or lower than[48,49] published literature values. Similarly, our published[50,51] and unpublished estimates of the test-retest reliability of dACC glutamate levels have been consistent across samples and acquisition methods (e.g., PRESS, MEGA-PRESS [i.e., Glx], 2d J-resolved PRESS), converging on a mean CV_{ws} of approximately 6.5%, which is also in line with[15] or lower than[52] published values. In sum, the present study was adequately powered and sensitive to detect hypothesized gabapentin effects on GABA and glutamate levels.

Procedure.

Written informed consent was obtained from every participant at a baseline evaluation appointment. Participants were screened for eligibility using the Structured Clinical Interview for DSM-5[53], and past 90-day cannabis use was assessed using the Timeline Followback (TLFB)[54] method. Cannabis use was recorded in times used/day, as well as quantity (e.g., grams, number of blunts/joints) to standardize for different types of cannabis

use. Participants were asked to quantify cannabis use by weighing out amounts of an inert cannabis surrogate and reporting on that amount's potency through dollar-value estimates[55]. Cannabis use was then expressed in grams per day for statistical analyses. Cannabis craving was measured using the 12-item, Marijuana Craving Questionnaire (MCQ)[56], and withdrawal symptoms were assessed using the Cannabis Withdrawal Scale (CWS)[57]. Mood symptoms were assessed using the YMRS/MADRS. Participants completed a history and physical examination and provided samples for blood chemistries and urine drug and pregnancy testing.

Following assessment, eligible participants completed two, 1-week experimental conditions (gabapentin, placebo) in randomized order. Each condition consisted of an in-person visit for assessment (repeating non-diagnostic baseline measures) and medication dispensation (Day 1), titration to maximum dose (i.e., 1200mg/day) (Days 1–5), assessment and MRI (Day 5; morning), immediately followed by medication-washout (Day 5 [afternoon]-Day 7) (see Supplemental Figure 2 for design schematic). Across each dosing period, 9 doses of gabapentin (doses 1–3=300mg, 4–9=600mg) or matched placebo were administered, with the first and final doses observed by study staff to ensure compliance, and with unused study medications returned for pill counts. A 5-day dosing period was chosen to minimize participant dropout while allowing sufficient time for participants to reach steady state concentrations of the target dose of gabapentin, given the medication's 6–7-hour elimination half-life[58]. Medications were packaged and dispensed by our Investigational Drug Service (IDS), a centralized research pharmacy that compounds medications. IDS oversaw blinding procedures for the study and maintained treatment-assignment records.

Participants were asked to abstain from cannabis and alcohol ≥12-hours prior to each MRI appointment. Participants who smoked cigarettes were allowed to have their last cigarette immediately prior to taking their final medication dose (approximately 1-hour pre-MRI). During structural and ^{1}H-MRS scanning, participants viewed scenic images via a mirror mounted to their 32-channel head-coil. Next, the Cannabis Cue Reactivity (CCR) task was administered[19]. Total scan time was 60–75-minutes in a Siemens 3.0T PrismaFit with actively-shielded magnet and high-performance gradients (80 mT/m, 200T/m-sec). The final medication dose was taken in the morning/early-afternoon of day 5, providing approximately 11 elimination half-lives prior to starting the subsequent condition[58].

^{1}H-MRS Acquisition and Processing.

A structural scan was taken for voxel placement and tissue segmentation (256 sagittal slices; 1mm thick/50% gap). ^{1}H-MRS data were acquired from dACC and rBG, which form an important frontostriatal reward circuit[59]. The dACC voxel was placed on midsagittal T1-weighted images, posterior to the genu of the corpus callosum, with the ventral edge of the voxel aligned with the dorsal edge of the callosum[60]. An rBG voxel was placed on an axial T1-weighted slice about 1-cm above the genu, between the Sylvian fissure and the lateral ventricles including corpus striatum[61]. Each voxel was 2.5×2.5×3cm^{3} to ensure adequate signal-to-noise. See Figure 1 for voxel locations and sample spectra. Following placement of saturation bands 1-cm away from voxel faces and shimming via FASTESTMAP, single-voxel water-suppressed ^{1}H-MRS spectra were acquired using

MEGA-PRESS (TR=2000ms; TE=68ms; number of averages=256) with editing-pulse frequencies symmetric with respect to water (1.9ppm and 7.5ppm)[47], and a PRESS sequence sensitive to glutamate (TR=2000ms; TE=40ms; number of averages=128)[62]. Unsuppressed water spectra were co-acquired for each sequence. MEGA-PRESS (GABA) data were processed using the Gannet MATLAB toolbox[63]. PRESS (glutamate) data were processed using LCModel 6.3[64]. Metabolites with fitting uncertainties <20% were retained. Water was quantified from a Gaussian-Lorentzian fit to the non-water-suppressed data. Within-voxel tissue-fractions of gray and white matter and cerebrospinal fluid (CSF) were calculated based on automated segmentation in Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Cognitive Neurology) using a volume mask generated in Gannet[65]. Metabolite concentrations were normalized to unsuppressed water and corrected for within-voxel CSF fraction.

fMRI Acquisition and Processing.

During the CCR task[19], participants were shown pseudorandomly-interspersed cannabis (cannabis plant, paraphernalia), neutral (e.g., pine cone, trumpet), and fixation-cross images. Cannabis and neutral images were matched by color, hue, and complexity. Stimuli were presented in six 90-s epochs, each consisting of three 24-s blocks (one block each of cannabis, neutral, and fixation). Participants rated their “urge to use marijuana” for 6-s after each block from 0 (“none”) to 4 (“severe”) via handpad. See Supplemental Figure 3a for task schematic. A Simultaneous Multi-Slice EPI sequence was acquired (parameters: # of simultaneously acquired slices=3; TR/TE=1200/30ms; flip angle=65°; field of view=213×213mm; voxel size=2.8×2.8mm; 51 contiguous 2.8-mm-thick slices). The main contrast of interest was activation during cannabis vs. neutral image blocks. fMRI analysis was completed in SPM12. Standard preprocessing including realignment, normalization, and smoothing was performed. Volumes were censored for motion correction and/or abrupt changes in global signal intensity using DVARS[66]. Both censored volumes and realignment parameters were included as nuisance regressors in 1st-level models which included cannabis, neutral, and hand-pad rating conditions with implicit baseline. Preprocessed data were analyzed within a general linear model mixed-effects framework. Following 1st-level analysis, subject-specific spatially-normalized contrast maps were entered into 2nd-level, whole-brain random-effects analyses. Because the validity of the CCR fMRI task in BD+CUD had not been previously demonstrated, we first estimated whole-brain activation of cannabis vs. neutral images across participants while on placebo. Condition parameter maps were cluster thresholded at z >2.58, family-wise-error (FWE, p<0.05) corrected for multiple comparisons.

Data Analysis.

General linear mixed-effects models, which used all available data per analysis, accounted for the potential effects of condition order (i.e., Order #1 – gabapentin first vs. Order #2 – placebo first) via the interaction between treatment condition (gabapentin vs. placebo) and scan number (1st scan vs. 2nd scan)[67]. Significant effects were followed up by pairwise comparisons where indicated. Baseline participant characteristics that differed between Randomization Orders (p<0.10) were tested as potential moderators of associations between treatment condition and MRI dependent variables (DVs). Additional exploratory moderators,

specified a priori in our proposal to examine associations of gabapentin-induced changes in GABA and glutamate with clinical outcomes, included cannabis use and YMRS and MADRS scores assessed at each visit. This analytic plan was executed for the primary DVs, dACC glutamate, GABA, rBG glutamate, GABA levels (^{1}H-MRS), as well as for the secondary DV, whole-brain activation to cannabis-minus-neutral images (fMRI). Correlations of activation in significant cue-activation clusters with cannabis use were estimated to evaluate clinical relevance. A nominal α of 0.05 was used to evaluate each test in this preliminary study.

RESULTS

Participant Retention, Adherence, and Adverse Events

Although 21 participants (95.5% of enrolled) completed the study, all 22 enrolled participants completed at least one MRI and were therefore evaluable for analysis. Medication adherence, determined via pill counts, was ≥94%. Gabapentin was very well-tolerated, with participants reporting more Adverse Events (AEs) while on placebo than gabapentin (11 vs. 7 AEs), and no participants reported Serious AEs or having to leave the study due to AEs. See Supplemental Table 1 for AEs by condition.

Baseline Participant Characteristics by Randomization Order

Evaluation of baseline participant characteristics by RO# (Table 1) revealed that participants in RO#2 had higher prevalence of anxiety disorder (p<0.01) and cigarette-smoking (≥10 cigarettes/day[68]; p=0.08), along with elevated MADRS scores (p=0.08) and cannabis use in the 90-days preceding baseline (p=0.03) relative to participants in RO#1. As a result, baseline smoking status, MADRS, and cannabis use were evaluated as potential moderators of associations between treatment condition and MRI DVs. Because RO#2 contained 100% of individuals with anxiety disorders, evaluating this variable as a moderator was not possible. However, anxiety disorder was associated with, and may have been responsible for, the elevated MADRS scores (ps=0.07–0.09) and cannabis use (p=0.05) observed in RO#2.

Primary Outcomes: ^{1}H-MRS Glutamate and GABA Levels

Quality-control evaluation of ^{1}H-MRS spectra (blind to condition) resulted in some data loss, making the number of cases available for analysis (by brain region/metabolite): dACC glutamate n=22, GABA n=21, rBG glutamate n=19, GABA n=20. Gabapentin increased dACC glutamate levels, but only in RO#1 (Figure 2); a significant interaction of treatment condition with scan number was found (F=9.42, p<0.01). Gabapentin increased rBG glutamate levels, but only in cigarette-smoking participants (Figure 3a); significant interaction of treatment condition and cigarette-smoking status was found (F=4.31, p=0.05). This interaction was likely due to the lower glutamate levels observed in cigarette-smoking participants (n=11) relative to non-cigarette-smoking participants (n=7; p=0.13, Cohen's d=0.75) while on placebo. Gabapentin failed to increase GABA levels across participants, as there were no significant main effects of treatment condition, nor interactions of condition with scan number, found for dACC or rBG GABA levels. No further interactions of

condition with baseline moderators (smoking status, MADRS, cannabis use) were found in statistical models of dACC GABA or glutamate levels (*p*s>0.10).

Secondary Outcome: fMRI Activation to Cannabis Cues

fMRI data were not collected for 5 participants (insufficient time *n*=3, claustrophobia/discomfort *n*=2), leaving *n*=17 evaluable for fMRI analyses. When participants were on placebo, cannabis vs. neutral images were associated with activation in a number of brain regions associated with drug-cue reactivity (basal ganglia, posterior cingulate, thalamus, middle frontal gyrus, $z > 2.58$, FWE-corrected $p < 0.05$; Supplemental Figure 3b). Gabapentin increased cannabis-cue activation in the posterior midcingulate cortex (pMCC), relative to placebo, but only in cigarette-smoking participants (Figure 4); significant interaction of treatment condition with cigarette-smoking status was found in a cluster subsuming pMCC ($z > 2.58$, FWE-corrected $p < 0.05$, k=887, peak: x=3, y=−1, z=41). Across participants and conditions, increased cannabis-cue activation in pMCC was significantly associated with decreased cannabis use ($r = -.38$, p=0.03), demonstrating the potential clinical relevance of this finding. Since gabapentin was also found to increase rBG glutamate levels in cigarette-smoking participants, we evaluated the correlation of pMCC activation to cannabis cues with rBG glutamate and GABA levels by cigarette-smoking status, and found a positive association of pMCC cue activation with both rBG glutamate (r = 0.44, p = 0.08) and GABA (r = 0.66, p < 0.01) levels in cigarette-smoking, but not in non-cigarette-smoking (ps > 0.20), participants.

Exploratory Analysis of Associations of Gabapentin-induced Changes in dACC and rBG GABA and glutamate levels with Cannabis Use and Mood Symptoms During the Study

Though gabapentin failed to increase brain GABA levels across participants, elevations of dACC GABA in participants while on gabapentin versus placebo were associated with lower manic/mixed symptoms during the study, and vice versa (Figure 3b); significant interaction of treatment condition with YMRS scores was found (F=11.09, p<0.01). Elevations of dACC GABA levels in gabapentin-treated versus placebo-treated participants were also associated with lower depressive symptoms during the study, but only in RO#2 (Supplemental Figure 4a; significant 3-way interaction of condition, scan number, and MADRS scores was found, F=5.45, p=0.03). Furthermore, elevations of rBG glutamate levels in participants while on gabapentin versus placebo were associated with lower cannabis use during the study, but only in RO#2 (Supplemental Figure 4b; significant 3-way interaction of treatment condition, scan number, and cannabis use was found, F=6.81, p=0.02).

DISCUSSION

Results from this preliminary, randomized, double-blind, placebo-controlled, crossover, multimodal-MRI study of gabapentin for BD+CUD demonstrate that, a) gabapentin was well-tolerated with high adherence and strong retention, b) gabapentin increased dACC glutamate levels in participants with lower levels of substance use and mood symptoms, c) gabapentin increased rBG glutamate levels and pMCC activation to cannabis cues in cigarette-smoking participants, and d) elevated rBG glutamate and dACC GABA levels

in participants while on gabapentin were associated with decreased cannabis use and mood symptoms in those with more severe substance use and mood symptoms. Together, these preliminary findings provide foundational support for gabapentin as a candidate adjuvant medication to therapeutically modulate brain GABA/glutamate levels in BD+CUD warranting further investigation.

Though promising, these findings must be interpreted with caution due to three interrelated limitations – relatively small sample size, randomization-order effects, and between-randomization-order differences in baseline characteristics. Although order effects may have genuinely reflected the effect of receiving gabapentin 1st versus 2nd on study outcomes, they more likely reflected the failure of simple randomization, due in part to small sample size, to balance condition orders on highly-impactful baseline characteristics. Cigarette-smoking status and anxiety disorder diagnosis, though specified *a priori* as moderators-of-interest in our proposal, were also evaluated due to significant between-randomization-order differences on these variables. Their impact on gabapentin-induced changes in brain GABA and/or glutamate levels was predicted because both have been associated with disturbances in GABAergic and/or glutamatergic transmission that are purported to be central to their phenomenology[69,70], as well as worse clinical outcomes in individuals with BD+CUD relative to those who do not smoke cigarettes[71] and do not have anxiety disorders[72]. Going forward, urn-randomization[73] by smoking status and anxiety disorder in a larger sample, in conjunction with a parallel-group (between-subject) study design to rule out potentially-genuine order effects, will be critical to overcoming the interpretational challenges presented by the findings of this preliminary study.

In addition to these limitations, we did not predict that effects of gabapentin on brain metabolites would be specific to glutamate and not GABA[29–32]. However, studies that reported an effect of chronic gabapentin dosing on increasing brain GABA levels have generally evaluated a higher dose of gabapentin (≥1800mg/day vs. 1200mg/day) over a longer period of time (≥2-weeks vs. 5-days). The excellent tolerability of gabapentin in the present study suggests that we could safely increase gabapentin dosing from 1200mg/day to 1800mg/day. Likewise, our high participant-retention rate (95.5%), combined with a parallel-group design, suggests we could increase the dosing duration from 5- to 14-days without suffering significantly-more participant dropout. These changes would arguably increase our chances of observing a gabapentin effect on GABA levels. Alternatively, gabapentin-related changes in brain GABA levels may have been masked by co-edited macromolecular signals or unaccounted for menstrual-cycle-related variability in female participants[47]. These potential confounds could also be addressed in future studies. Provided these combined changes, if gabapentin still failed to increase GABA levels in BD+CUD (e.g., due to the concurrent effects of ongoing cannabis use), we may more-confidently conclude that observed neurobehavioral effects of gabapentin on BD+CUD are better explained by changes in glutamate transmission[33].

Results from the CCR fMRI task added richness to the findings of the present study. In cigarette-smoking participants, gabapentin increased pMCC activation to cannabis cues which was, in turn, associated with decreased cannabis use during the study. Though interesting, we did not anticipate the effect of gabapentin on cannabis-cue brain activation

to be facilitatory nor localized to the pMCC, as this region has not been identified as part of the cannabis-cue activation network by this study or others[19]. Instead, pMCC is central to recruitment of attentional-control circuitry to guide body orientation and reflexive movements in response to sensory stimuli, including rewards[74,75]. Nonetheless, behavioral manifestations of pMCC function include successful response inhibition while viewing emotionally-valenced images[76], and people with BD (relative to healthy control subjects) exhibit significantly-less pMCC activation to cognitive-interference demands when exposed to similar experimental conditions[77]. As such, the observed effect of gabapentin on increasing pMCC activation to cues, and inverse association of increased pMCC cue-activation and decreased cannabis use, may represent gabapentin-induced suppression of involuntary drug-seeking motor behaviors (i.e., disrupting the sequence of events) that typically culminate in cannabis use[67]. That gabapentin increased pMCC cannabis-cue activation in parallel with increased rBG glutamate levels, may further indicate a restorative balance of subcortical (and cortical) reward-circuitry function, mediated in part by glutamatergic projections from pMCC to rBG[78], in cigarette-smoking participants which could result in more adaptive behaviors. Finally, that these combined effects were relatively more pronounced in cigarette-smoking participants may reflect their substantially lower glutamate levels while on placebo, relative to non-cigarette-smoking participants, as observed in the present study[13,29,31]. Of course, this speculative interpretation requires empirical confirmation.

In addition to employing a more-robust study design, future studies of gabapentin in BD+CUD should evaluate a wider array of clinically-relevant phenomena, as gabapentin may indirectly reduce cannabis use by providing relief to symptoms of anxiety and sleep disturbance that drive persistent cannabis use[79,80]. Clinical trials of gabapentin for CUD[34] or AUD[81] have demonstrated that gabapentin may reduce mood and sleep disturbances, along with reducing drug use, in individuals with SUD. Furthermore, gabapentin has demonstrated efficacy in treating anxiety disorders[82–84], which are prevalent and impairing in individuals with BD+SUD[72,85], as well as sleep disturbance that occurs in the context of medical illness[86]; important because sleep disturbance is central symptom of, and potential trigger of, BD Mood Episodes[87], as well as an impairing symptom of protracted cannabis withdrawal[88]. Along with evaluating more clinical-symptom measures, future studies should also evaluate participants' motivation to reduce cannabis use. Most people with CUD do not seek treatment, with lack of motivation given as the predominant reason for not getting help[89]. However, participant-reported motivation to reduce/quit, and reasons for, cannabis use in BD+CUD individuals have never been reported. This information will be needed to successfully design and evaluate therapeutic interventions of any kind in this challenging clinical population.

In conclusion, despite the dire need for safe and efficacious treatments for BD+CUD, little is known about optimal treatment in this population. Convergent evidence supports disrupted brain GABA/glutamate homeostasis as a promising interventional target. Results from the present study support gabapentin as a candidate adjuvant medication to therapeutically engage that target, thereby reducing cannabis use, mood symptoms, and perhaps anxiety and sleep disturbance, in individuals with BD+CUD. Results from this study may guide the development and execution of larger, urn-randomized, parallel-group RCTs needed to

further realize the potential therapeutic promise of gabapentin for BD+CUD. These results also add to the literature on associations of brain GABA and glutamate levels with constructs related to BD and CUD (including cannabis-cue reactivity and use, cigarette-smoking, and mood symptomatology), and provide foundational demonstration of a neurobehavioral, multimodal-MRI platform for evaluating glutamatergic/GABAergic drugs for BD+CUD and other conditions marked by dysfunction of GABAergic and/or glutamatergic transmission (e.g., schizophrenia, anxiety disorders).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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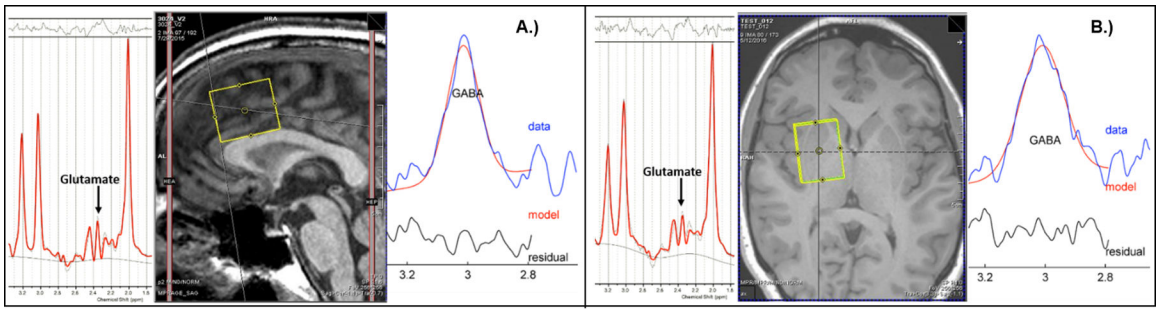

Figure 1.

A.) Sample dACC voxel (center), fitted PRESS glutamate spectrum (left), fitted MEGA-PRESS GABA spectrum (right). B.) Sample rBG voxel (center), fitted PRESS glutamate spectrum (left), fitted MEGA-PRESS GABA spectrum (right).

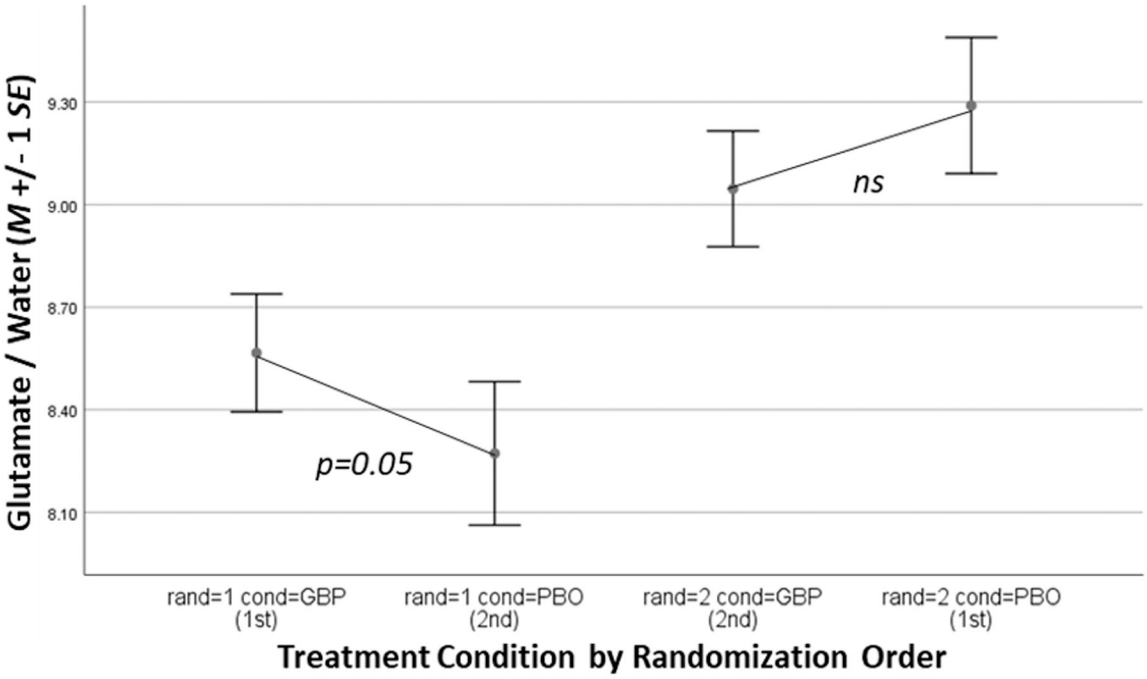

Figure 2.
dACC glutamate levels by treatment condition (GBP=gabapentin, PBO = placebo) and randomization order (rand).

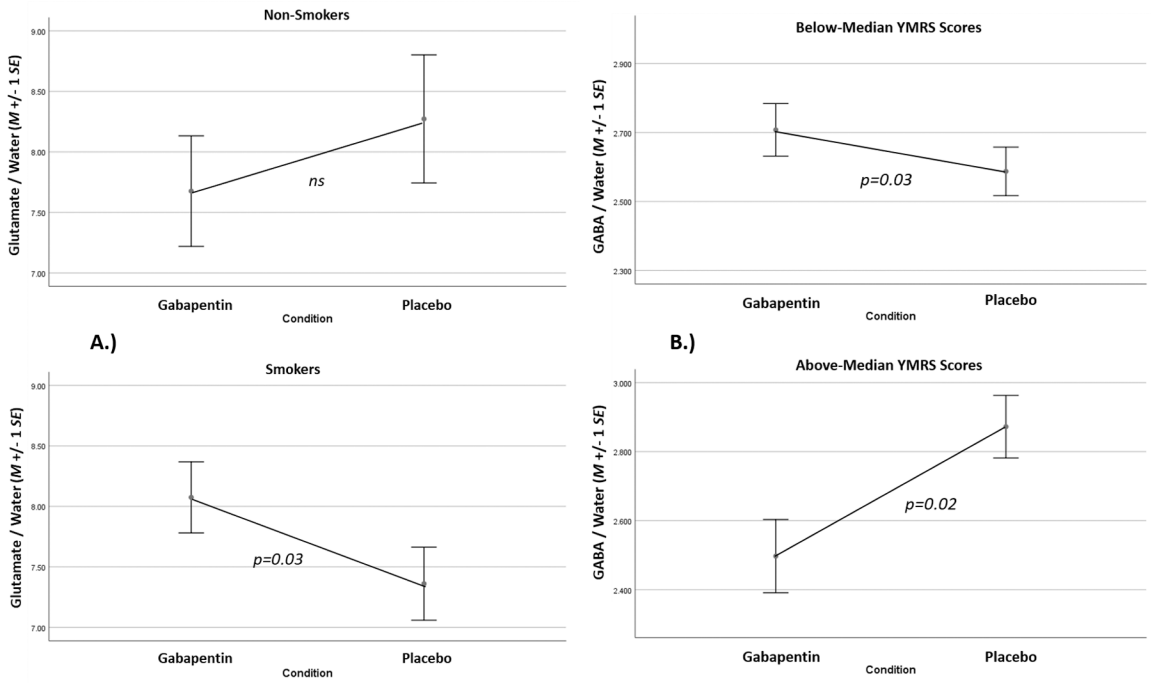

Figure 3.

A.) rBG glutamate levels by treatment condition and smoking status (top=non-smokers, bottom=smokers). B.) dACC GABA levels by treatment condition and YMRS scores during the study (top=below-median YMRS, bottom=above-median YMRS).

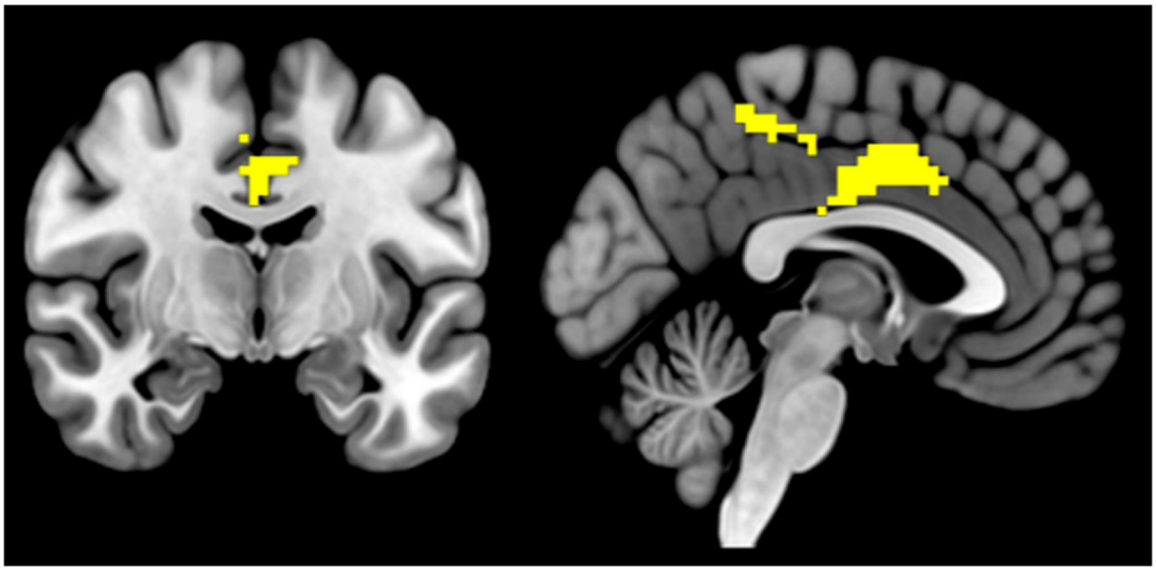

Figure 4.

Posterior midcingulate cluster, in which gabapentin increased activation to cannabis cues, but only in cigarette-smoking participants ($z > 2.58$, FWE < 0.05, $k = 640$ voxels, center [x,y,z] = 1.9, −16.6, 42.2).

Table 1

Baseline participant characteristics and comparison by randomization

	Overall Sample (*n* = 22)	Randomization 1 (*n* = 11)	Randomization 2 (*n* = 11)	*p*
Age (in years), *M (SD)*	37.59(11.91)	38.55(11.41)	36.63(12.86)	0.717
Sex, *n* (%)	11(50%)	5(45.5%)	6(54.5%)	0.670
Smoking status, *n* (%)	13(59.1%)	4(36.4%)	9(81.8%)	0.080 †
Anxiety Disorder, *n* (%)	7(31.8%)	0(0.0%)	7(63.6%)	0.004 *
BD sub-type, *n* (%) I	12(54.5%)	6(54.5%)	6(54.5%)	1.000
YMRS, *M (SD)*	4.00(3.98)	2.91(3.33)	5.09(4.41)	0.206
MADRS, *M (SD)*	8.27(7.86)	5.36(4.43)	11.18(9.56)	0.082 †
Cannabis Withdrawal Scale, *M (SD)*	36.73(32.99)	36.45(37.37)	37.00(29.81)	0.970
Marijuana Craving Quest., *M (SD)*	37.41(17.07)	36.18(15.38)	38.64(19.29)	0.745
Cannabis use (grams/day), *M (SD)*	3.00(3.41)	1.47(2.32)	4.52(3.72)	0.032 *
Medication (%)				
Lithium	4(18.2%)	2(18.2%)	2(18.2%)	1.000
Antipsychotic	18(81.8%)	8(72.7%)	10(90.9%)	0.586
Anticonvulsant	9(40.9%)	4(36.4%)	5(45.5%)	1.000
Antidepressant	9(40.9%)	4(36.4%)	5(45.5%)	1.000

χ^2 (categorical variables) tests, using Fisher's Exact when applicable, and independent samples t-tests (continuous variables) were performed.

BD = bipolar disorder; YMRS, Young Mania Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; Quest. = Questionnaire.

† $p < 0.10$;

* $p < 0.05$.