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Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder

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CONFLICT OF INTEREST

In the past 5 years, Dr. Murrough has provided consultation services to Sage Therapeutics, Novartis, Allergan, Fortress Biotech, Janssen Research and Development, Genentech, MedAvante-ProPhase, and Global Medical Education (GME) and has received research support from Avanir Pharmaceuticals, Inc. Dr. Murrough is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders. The Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine if it is approved for the treatment of depression. Dr. Murrough is not named on this patent and will not receive any payments. Dr. Collins has received consulting fees from MedAvante-ProPhase for services unrelated to this study. In the past three years, Dr. Pizzagalli received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehreinger Ingelheim, Pfizer, and Posit Science for activities unrelated to the present study. In the past three years, Dr. Iosifescu has provided consultations to Alkermes, Axsome, MyndAnalytics (CNS Response), Jazz, Lundbeck, Otsuka, Sunovion, and has received research support (through his academic institutions) from Alkermes, Astra Zeneca, Brainsway, LiteCure, Neosync, Roche, and Shire. All other authors declare no conflicts of interest.

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Abstract

Major depressive disorder (MDD) is a leading cause of disability worldwide, yet current treatment strategies remain limited in their mechanistic diversity. Recent evidence has highlighted a promising novel pharmaceutical target—the KCNQ-type potassium channel—for the treatment of depressive disorders, which may exert a therapeutic effect via functional changes within the brain reward system, including the ventral striatum. The current study assessed the effects of the KCNQ channel opener ezogabine (also known as retigabine) on reward circuitry and clinical symptoms in patients with MDD. Eighteen medication-free individuals with MDD currently in a major depressive episode were enrolled in an open-label study and received ezogabine up to 900 mg/day orally over the course of ten weeks. Resting state functional magnetic resonance imaging data were collected at baseline and post-treatment to examine brain reward circuitry. Reward learning was measured using a computerized probabilistic reward task. After treatment with ezogabine, subjects exhibited a significant reduction of depressive symptoms (Montgomery-Asberg Depression Rating Scale score change: −13.7±9.7, $p<0.001$, $d=2.08$) and anhedonic symptoms (Snaith-Hamilton Pleasure Scale score change: −6.1±5.3, $p<0.001$, $d=1.00$), which remained significant even after controlling for overall depression severity. Improvement in depression was associated with decreased functional connectivity between the ventral caudate and clusters within the mid-cingulate cortex and posterior cingulate cortex (n=14, voxel-wise $p<0.005$). In addition, a subgroup of patients tested with a probabilistic reward task (n=9) showed increased reward learning following treatment. These findings highlight the KCNQ-type potassium channel as a promising target for future drug discovery efforts in mood disorders.

INTRODUCTION

Depression is a leading cause of disability worldwide [1]. Available treatments, however, are only partially effective for many patients [2] and are associated with additional limitations, including a slow onset of therapeutic action and undesirable side effects [3,4]. Currently, the Food and Drug Administration (FDA)-approved treatments for depression, mostly consisting of serotonergic and noradrenergic agents, largely share the same basic pharmacology and mechanism of action based on decades-old discoveries [5]. This lack of mechanistic diversity leaves little opportunity for improved patient outcomes or personalized treatment approaches. In contrast, rational drug discovery based on a mechanistic understanding of disease pathology promises to deliver more effective, targeted therapies [6].

Recent preclinical evidence has highlighted the KCNQ-type voltage-gated potassium channel as a promising novel molecular target for the treatment of depression in a well-validated mouse model of depression—chronic social defeat stress (CSDS) [7,8]. CSDS produces two distinct phenotypes—susceptible and resilient—determined by the defeated mouse's willingness to interact with a novel mouse. CSDS results in an increased firing rate

of ventral tegmental area (VTA) dopamine neurons projecting to the nucleus accumbens (NAc) within the ventral striatum (VS) in rodents expressing a pro-depressive phenotype [7,9]. Critically, resilient animals also exhibit dysregulation within this circuit; however, they are able to actively counteract VTA-NAc hyperactivity by upregulating the KCNQ3 potassium channel within the VTA [7], which serves to rebalance dopaminergic firing [10]. Replicating this active mechanism in susceptible mice via viral overexpression of KCNQ3 within the reward circuit reverses the depressive behaviors, leading to a more resilient phenotype in rodents. Of translational importance, systemic injection of ezogabine, a KCNQ-selective potassium channel opener, also led to the amelioration of depressive behaviors in susceptible mice [8]. Taken together, this work supports the hypothesis that enhancing activity at KCNQ channels within the reward circuit may represent a novel mechanistic approach to antidepressant treatment discovery.

Based on these findings, we conducted a 10-week open-label pilot of ezogabine with the aim of determining if ezogabine significantly engages the reward system in human patients with MDD. Connectivity of the reward system was measured using resting state functional magnetic resonance imaging (fMRI) with the VTA and VS as regions of interest for resting state functional connectivity (RSFC) analysis. In addition, clinical anhedonia and reward learning were examined using the Snaith-Hamilton Pleasure Scale (SHAPS) and the probabilistic reward task (PRT) [11], respectively. Consistent with the hypothesis that ezogabine functions to strengthen resilience to stress [12], changes in resilience were measured using the Connor-Davidson Resilience Scale (CD-RISC) [13]. We hypothesized that modulation of the KCNQ potassium channel in humans would parallel the antidepressant effects found in animals, especially within the domain of reward system function, and would additionally normalize the connectivity of brain circuitry involved in depressive symptomatology. In order to assess the specificity of the effect of ezogabine on brain circuitry, we conducted a parallel analysis of changes in VTA and VS RSFC associated with antidepressant response to the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine in a separate group of adult patients with MDD.

MATERIALS AND METHODS

Ezogabine’s Pharmacology, Brain Exposure, Safety, and Tolerability

Ezogabine is a first-in-class KCNQ-selective potassium (K+) channel opener approved by the U.S. Food and Drug Administration (FDA) for the adjunctive treatment of partial-onset seizures. Ezogabine selectively binds to and activates KCNQ transmembrane K+ ion channels, thereby enhancing transmembrane potassium currents mediated by the KCNQ (Kv7.2 to 7.5; e.g., KCNQ2/3) family of ion channels. By activating KCNQ channels, ezogabine is thought to stabilize the resting membrane potential and reduce brain excitability, likely leading to the observed anticonvulsant effect. Ezogabine is rapidly absorbed in 0.5 and 2 hours and readily crosses the blood-brain barrier at physiological concentrations and is fully metabolized primarily via glucuronidation and acetylation in humans with a half-life between 7 to 11 hours. The efficacy of ezogabine as adjunctive therapy in partial-onset seizures was established in three multicenter, randomized, double-blind, placebo-controlled studies in 1,239 adult patients. The most common adverse effects

of ezogabine are dizziness (23%), drowsiness (22%) and fatigue (15%). No contraindications to treatment were reported in the manufacturer's label. Since QT prolongation has been observed, ECG was monitored before, during and after the treatment with the study drug. Skin discoloration around the lips or nail bed, either blue or gray, has been reported and is estimated to affect up to 10% of patients treated for more than two years. Ezogabine carries a black box warning regarding the potential for retinal abnormalities following treatment with ezogabine, with an unknown relationship to vision loss. In June 2015, the FDA issued a safety alert stating that there was no evidence for treatment-associated vision loss. In keeping with FDA recommendations, study participants underwent full ophthalmological exams at screening and study exit [14–17]. Other side effects include urinary retention, neuropsychiatric symptoms (confusional state, psychotic symptoms, and hallucinations) and withdrawal seizures.

Study Participants and Design

The current study recruited 18 subjects 18–65 years of age with a primary diagnosis of MDD as assessed by the Mini-International Neuropsychiatric Interview [18]. Additional inclusion criteria were a score of 21 or greater on the Montgomery-Asberg Depression Rating Scale (MADRS) [19] and a score of at least 20 on the SHAPS [20], indicating moderate depression and anhedonia severity, respectively. Individuals were excluded if they had a lifetime history of schizophrenia, bipolar or psychotic disorder, substance use disorder in the preceding 6 months, unstable medical condition, retinal abnormalities, active suicidal or homicidal ideation, or current use of any psychotropic medications. Every subject underwent physical examination, clinical hematological and biochemical screening, urine toxicology testing, and electrocardiogram. Study participants were free of concomitant psychotropic medications for at least 2 weeks (4 weeks for fluoxetine) prior to commencement and for the duration of the study, with exceptions being a stable dose of zolpidem 10 mg nightly for sleep or a benzodiazepine for sleep or anxiety (dosage equivalent to lorazepam 1 mg daily or less). As part of the screening procedures and during the course of the study (midway through the treatment with ezogabine, and two weeks post-cessation of the drug), participants underwent an ophthalmological exam according to the FDA recommendation, as ezogabine carries a black box warning for retinal abnormalities with similar features to retinal pigmental dystrophies. In addition, an electrocardiogram was completed midway through and at study end in order to monitor for QT interval prolongation, which is reported to occur with the study drug.

All study procedures were conducted at the Icahn School of Medicine at Mount Sinai in New York City. The institutional review board at Icahn School of Medicine at Mount Sinai approved the study, and written informed consent was obtained from all participants prior to any study procedure. Participants were compensated for their time and effort. The study is registered at clinicaltrials.gov (NCT02149836). Following screening, study subjects completed a pre-treatment assessment that included the PRT [11] and fMRI scanning (details below). Participants who completed the pre-treatment assessment and continued to meet all inclusion/exclusion criteria entered the treatment period. During this phase, ezogabine was titrated following the FDA guidelines until reaching the maximum target dose of 300mg three times daily (900mg/day) at week four. Subjects were required to

tolerate a minimum dose of 600mg/day in order to continue in the study. At each visit, participants completed self-report and clinician-administered rating scales performed by trained raters, and met with a study psychiatrist. The treatment period consisted of eight study visits, which culminated in the primary post-treatment visit, where participants received a second and final PRT assessment and fMRI scan. Following this visit, participants were instructed to taper the study medication over the following three weeks based on FDA-recommended guidelines and returned to the clinic for a final study exit visit. The primary clinical post-treatment of the study was depression severity as measured by the MADRS administered by a trained rater. Depression was additionally measured using the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) [21], and global illness severity was measured using the Clinical Global Impression-Improvement/Severity (CGI-I/S) [22]. Anhedonia was measured using the SHAPS and the Temporal Experience of Pleasure Scale (TEPS) [23]. Resilience was measured by the CD-RISC [13]. Safety and tolerability were assessed at each study visit by frequency of adverse events (AEs) and suicidal ideation and behavior by the Columbia Suicide Severity Rating Scale (C-SSRS) [24]. Medication compliance was calculated via medication reconciliation forms and pill count. AEs were reported according to the Medical Dictionary for Regulatory Activities (MeDRA) system [25].

Statistical Analysis of Clinical Data

Demographic data and clinical characteristics were analyzed using summary statistics. Given the small sample size, last observation carried forward (LOCF) was used for intent-to-treat (ITT) analysis. Paired two-sided t-tests between pre-treatment (week 0) and post-treatment (week 10) were performed on self-report questionnaires and clinician-administrated scales. For instruments with more than two time points available for analysis, repeated measures analysis of variance (ANOVA) was performed. A $p<0.05$ was considered statistically significant and Bonferroni correction was utilized for repeated measures ANOVA analyses. No adjustment was made for multiplicity across clinical measures. The proportion of patients who achieved response and remission criteria was also computed, defined as a 50% reduction in MADRS score at study end compared to pre-treatment or a MADRS score below 10, respectively.

fMRI Data Acquisition, Processing, and Analysis

Imaging data were acquired using a Siemens 3T Connectome Skyra scanner (Siemens, Erlangen, Germany) with a 32-channel headcoil. A T1-weighted anatomical image was acquired at 0.8mm isotropic resolution (TR=2400ms, TE=2.07 ms, Flip Angle=8°). Resting state fMRI data were acquired as a set of 600 gradient-echo echo-planar images with 70 axial slices (2.1mm isotropic resolution, no gap, TR=1,000 ms, TE=35ms, flip angle=60°, multiband factor=7) for 10 minutes with eyes open. Resting state fMRI data were processed using a combination of AFNI [26] and FSL [27] tools. Data were despiked, motion corrected and co-registered to their respective anatomical image. Independent component analysis-based motion denoising was performed with ICA-AROMA [28]. Signal from white matter and cerebrospinal fluid were regressed out [29]. Functional data were normalized to MNI space and spatially smoothed with a 6mm full-width-at-half-maximum (FWHM) kernel. Finally, volumes were band-pass filtered between 0.01 and 0.1 Hz and detrended.

Seed-to-whole-brain resting state functional connectivity (RSFC) was computed at pre-treatment and post-treatment for three regions of interest: VTA, defined functionally [30], and bilateral ventral caudate (vCa) and NAc, defined anatomically by the Harvard-Oxford Atlas distributed with FSL (see Figure 2d for seeds). Within the reward circuit, we focused on the striatal seeds, in part due to limited signal availability at the level of the VTA [31]. For these analyses, we primarily examined RSFC changes that were associated with clinical improvement [(post-treatment – pre-treatment RSFC) × (post-treatment – pre-treatment MADRS/SHAPS)]. We secondarily examined (a) RSFC changes from pre-treatment to post-treatment; (b) pre-treatment RSFC correlations with pre-treatment clinical measures; (c) pre-treatment RSFC correlations with changes in clinical measures. These analyses were performed as paired or one sample two-sided t-tests with clinical measures as covariates of interest, and sex and age as nuisance covariates. For seed-to-whole-brain analyses, cluster-defining thresholds were computed at an alpha level of <0.05 using AFNI's method of permutation testing. For voxelwise p's<0.01, this method adequately controls the false positive rate <5% and addresses the concerns that have been raised with significance testing of fMRI data [32,33]. We reported findings as significant for a voxelwise p<0.005, for which the minimum significant cluster size was determined to be 137 voxels. For the primary aim, Bonferroni correction was performed for a total of four comparisons (two seeds vs. change in MADRS/SHAPS). Pearson's correlations between the mean RSFC of significant clusters and clinical measures were computed and then converted to corrected p values.

In order to assess if the primary findings are specific to the pharmacology of ezogabine, parallel analyses were performed on a group of 15 adult individuals with MDD who received a single intravenous (IV) infusion of ketamine (0.5 mg/kg) in the context of a separate clinical trial (clinicaltrials.gov; NCT01880593). These subjects received pre- and post-treatment scans with identical acquisition parameters, preprocessing pipelines, and analytic strategy as the subjects in the ezogabine protocol. Likewise, subjects in the ketamine protocol were free of concomitant antidepressant treatment and in a current major depressive episode. See Supplemental Material for further detail.

Probabilistic Reward Task

The PRT is a signal detection test that provides an objective assessment of reward learning [11]. During this computer-based task, subjects are asked to discriminate between two ambiguous stimuli – a short (11.5 mm) vs. long (13 mm) mouth displayed rapidly (100 ms) in a schematic face – in order to receive a monetary reward of 20¢. Unbeknownst to the subjects, correct identification of one stimulus (the "rich stimulus") is reinforced three times more frequently than the other stimulus (the "lean stimulus"). Under these experimental circumstances, healthy subjects reliably develop a response bias for the rich stimulus, regardless of which stimulus was actually presented. Contrarily, subjects with MDD fail to develop this bias for the more frequently reinforced stimulus, and tend to respond similarly to both stimuli, reflecting decreased responsiveness to rewards. Discriminability was also calculated as a measure of more general task performance. Response bias and discriminability were computed using the following formulae:

$$\text{Response bias: } \log b = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}}\right)$$

$$\text{Discriminability: } \log b = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}}\right)$$

The task consisted of three 100-trial blocks and was programmed in E-Prime (Version 1.1; Psychology Software Tools, Inc., Pittsburgh, PA). To avoid practice effects in repeated measures designs, two separate versions of the PRT were used and randomly assigned. The parameters were identical except that the target stimuli were discriminated by mouth size or nose size [34].

Prior to data analysis, PRT data underwent a quality control check wherein trials with below chance accuracy and/or >10% reaction time outliers were excluded from analysis. The measure of interest was change in response bias across the three Blocks of the task, as a function of Time (pre-treatment to post-treatment), as analyzed by repeated measures *Block* × *Time* ANOVA. Change in discriminability was also examined in order to ensure that increases in response bias were not associated with general improvements in task performance [11,35]. Pearson's correlations between pre-treatment response bias (averaged over the latter two blocks of the task, after learning has occurred) and changes in clinical measures were computed to test for associations with treatment response.

RESULTS

Sample Characteristics

Of the 26 subjects assessed for eligibility, 18 met all inclusion/exclusion criteria and were enrolled and constituted the intent-to-treat (ITT) sample (age 51.1±9.1, 13 male). Subjects were in their current major depressive episode (MDE) for an average of five years and had a median of three lifetime MDEs; 13 had experienced recurrent MDD (Table 1). Pre-treatment MADRS score ranged from 21 to 38, and pre-treatment SHAPS score ranged from 27 to 51. Of the 18 individuals, 17 completed all study visits. One participant elected to discontinue the study after six weeks of treatment for unspecified reasons; all other participants completed the study. Across the whole sample, compliance with study medication as measured by pill count was 97%.

Symptom Change and Tolerability

Depressive symptoms decreased significantly from pre-treatment (week 0) to post-treatment (week 10) (MADRS mean change: −13.7±9.6, t_{17}=−6.01, p<0.001, Cohen's d=2.08) and throughout the study as a function of time (RM-ANOVA: $F_{3,52}$=21.96, p<0.001, partial-η^2=0.56; Figure 1a). Pairwise comparisons showed a significant improvement from week three onwards (all p's<0.001, Bonferroni adjusted), relative to pre-treatment. Overall, after ten weeks of treatment, patients showed a 45% (SD=28.9) reduction in MADRS score from pre-treatment to post-treatment. Likewise, QIDS-SR score was significantly reduced at study

end compared to pre-treatment (mean change: −5.72±4.4, t_{17} =−5.53, p<0.001, Cohen's *d*=1.64). Eight out of 18 (44%) and 5 out of 18 (28%) of patient met response and remission criteria, respectively.

Eleven out of 18 (61%) of patients were classified as 'much improved' or 'very much improved' according to the CGI-I (Figure 1b). There was a significant improvement in anhedonia from pre-treatment to post-treatment (SHAPS mean change: −6.1±5.3, $t_{17=}$4.8, p<0.01, Cohen's *d*=1.00) and throughout the study as a function of time ($F_{5,85=}$11.84, p<0.001, partial-η^2=0.41), which remained after controlling for depression severity measured by the change in MADRS score calculated without the item related to anhedonia (Item 8: Inability to feel) ($F_{5,80=}$3.03, p=0.015, partial-η^2=0.16). Finally, study participants showed an improvement in resilience (CD-RISC mean change: 8.2±12.2, $t_{17=}$2.9, p<0.01; pairwise comparison $F_{3,52=}$3.61, p=0.02, partial-η^2=0.17, Bonferroni adjusted) (Table 2).

The most common AE was dizziness, which occurred in 8 subjects. Less frequent AEs were confusion and headache that were reported in 3 and 2 participants, respectively. Due to the occurrence of AEs, three study participants failed to achieve the highest dose (900 mg/day) and remained at 750 mg/day (n=1) and 600 mg/day (n=2). No subjects discontinued the treatment protocol because of AEs, and no serious adverse events occurred during the course of the study. No incidents of retinal abnormalities were observed at ophthalmologist visits. A summary of AEs is reported in Table S1 of the supplementary material. No increase in suicidal ideation as measured by the C-SSRS was reported during the treatment with ezogabine and no participants experienced emergence of suicidal behavior during the study trial.

Resting State Functional Connectivity

Of the 18 subjects enrolled, 16 had a pre-treatment fMRI scan, and 14 had both a pre-treatment and post-treatment fMRI scan. In our primary analysis, we found that improvement in depressive symptoms (MADRS) from pre-treatment to post-treatment was significantly associated with a reduction in connectivity between vCa and clusters within the mid-cingulate cortex (MCC) (peak z=−4.29, k=189, corrected p=0.008) and the posterior cingulate cortex (PCC)/precuneus (peak z=−3.82, k=170, corrected p=0.008; Figure 2a). Improved anhedonia (SHAPS) was similarly associated with reduced connectivity between vCa and both MCC (peak z=−4.87, k=411, corrected p=0.004) and PCC (peak z=−3.78, k=182, corrected p=0.13; Figure 2b). All results except the association between change in vCa-PCC RSFC and change in SHAPS survive Bonferroni correction. In the ketamine group, there were no significant associations between changes in vCa RSFC and changes in symptoms at the whole brain level. Furthermore, there were no significant associations between changes in vCa RSFC with the clusters reported above and respective changes in clinical measures (all p's>0.4) (Supplementary Material Figure S2).

In our secondary analyses, we found that greater pre-treatment connectivity between vCa and MCC was significantly associated with greater improvement in depressive symptoms from pre-treatment to post-treatment (peak z=3.79, k=164; Figure 2c) (all voxel-wise p<0.005, cluster-wise α<0.05; Figure 2; MNI coordinates of cluster peaks are reported in Supplementary Material Table S2).

There were no significant associations between NAc or VTA connectivity changes and symptom changes and there were no significant connectivity changes from pre-treatment to post-treatment or associations between pre-treatment connectivity and pre-treatment clinical measures.

Reward Learning

Sixteen subjects completed the PRT at both pre-treatment and post-treatment. Of these, twelve had valid pre-treatment data and nine had valid pre-treatment and post-treatment data. The *Block* × *Time* ANOVA revealed a main effect of *Block*, ($F_{2,16=}$5.38, p=0.02, η^2=0.40), where across both time points, response bias increased from blocks one to three of the task. A main effect of *Time* also emerged ($F_{1,8=}$6.34, p=0.04, η^2=0.44), where across blocks, response bias was found to be significantly higher at post-treatment compared to pre-treatment (Figure 3a), indicating improved reward learning. No significant interaction or main effects emerged from the *Time* × *Block* ANOVA on discriminability (a measure of subject's ability to discriminate between the stimuli that is unrelated to the asymmetrical reinforcement ratio), indicating that increases in response bias from pre-treatment to post-treatment were not simply due to general improvements in task performance (all p's>0.05). Finally, higher pre-treatment response bias averaged across the latter two blocks of the task (after learning has taken place) was associated with a greater reduction in SHAPS score from pre-treatment to post-treatment (r=0.64, p=0.02) (Figure 3b). This association was not observed with changes in overall depression severity on the MADRS (r=0.46, p=0.13), suggesting that pre-treatment response bias was specifically associated with treatment-related improvements in anhedonia, but not in depressive symptoms more generally.

DISCUSSION

In the current study, we report that ezogabine, a first-in-class KCNQ channel opener, is associated with improvement in symptoms of depression and anhedonia in patients with MDD in the context of an open-label design. The improvement in anhedonia remained significant after controlling for change in non-anhedonia depressive symptoms, indicating that ezogabine may specifically target the symptom of anhedonia. A significant increase in resilience was observed, consistent with the hypothesis that ezogabine functions to strengthen resilience to stress [12]. Ezogabine was well tolerated in this sample; no SAEs occurred and no subjects discontinued the treatment due to AEs. Improvements in depression and anhedonia were associated with a reduction in functional connectivity between the vCa and both the MCC and the PCC at the whole-brain level, corrected. Finally, subjects showed evidence of increased reward learning following treatment, which may indicate a potential reversal of a reward learning deficit known to be associated with depression [35,36]. It is important to note that due to the open-label nature of this study, we are unable to conclude if these changes are due to the pharmacological effects of ezogabine or to non-specific factors, such as the placebo effect or natural variation in the underlying depression. In a separate group of patients with MDD who were treated with a single infusion of ketamine, we did not observe any changes in vCa connectivity associated with clinical improvement. These findings provide a preliminary indication that ezogabine may indeed be specifically targeting the reward system and subsequent randomized controlled

trials examining the effects of ezogabine or other KCNQ channel potentiators on neurobehavioral measures linked to depression are thereby warranted.

The current findings are consistent with the recent preclinical work that provided the theoretical grounds for this study. The KCNQ potassium channel was selected as a pharmacological target for the treatment of depression because it was upregulated in VTA dopamine neurons exclusively in mice resilient to CSDS. Both susceptible and resilient animals exhibit elevated VTA dopamine neuron excitability after CSDS, but only resilient animals actively engaged gene regulation mechanisms in order to reverse the phenotype [7–10]. This belies the common characterization of resilience as the lack of pathological alteration. Rather, one major feature of resilience may be to actively reverse pathology. Induction of this active resilience mechanism in previously susceptible mice—either via upregulation of the KCNQ channel expression with viral vectors or enhancing existing channels with a KCNQ potentiator such as ezogabine—was capable of reversing their depressive symptoms. Our findings are also potentially consistent with preclinical studies that have demonstrated an association between increased BDNF release and synaptogenesis within the VS/NAc and depressive behaviors [37,38]. The results of the present study provide a preliminary demonstration for this approach and argue for the development of KCNQ channel potentiators that are more selective for channel isoforms enriched in the VTA and other limbic brain structures.

Effects of ezogabine appear to relate to modulation of a striatal-mid cingulate network. Although it has been argued that affective functions are localized to the rostral cingulate, while cognitive and motor functions are localized to the MCC [39,40], recent observations have implicated the MCC in a diverse array of functions including pain, negative affect and social processing [41,42]. The MCC is heavily connected with the caudate and the midbrain dopaminergic system, which are implicated not only in the incentive salience of appetitive, but also aversive stimuli [43–45]. Indeed, depressed patients show greater connectivity between the ventral striatum and MCC during loss versus win and disappointment versus win processing in a reward task [46]. Overall, the MCC seems to act as a hub that integrates affective information with cognitive control and motor centers for the expression of goal-directed behavior [41]. Taken together, our data suggest that ezogabine may function by facilitating decoupling between the ventral striatal reinforcement and MCC pain and negative affect systems.

The current study also implicated the PCC and precuneus in the neurobiological effects of ezogabine. These regions are the posterior elements of the default mode network and are thought to support episodic recollection while subjects engage in spontaneous cognition [47]. In an activation likelihood estimate meta-analysis of resting state fMRI in MDD, the anterior precuneus was found to be hyperactive [48]. Additionally, default mode dominance over task positive networks has been associated with a tendency towards maladaptive rumination as opposed to adaptive reflection[49]. Compared to healthy controls, depressed subjects exhibit elevated PCC response to emotional stimuli [50], and similar to the MCC, depressed subjects exhibit increased connectivity between the ventral striatum and precuneus during disappointment versus win processing in a reward task [46]. As with the MCC, we propose that ezogabine may function by decoupling the ventral striatal

reinforcement system from the PCC and precuneus, regions associated with maladaptive rumination and dysfunctional reward and emotional processing.

Ezogabine significantly improved reward learning as measured by the PRT. Subjects with MDD and healthy subjects with depressive symptoms show evidence of a more blunted response bias on this paradigm, reflecting a decreased responsiveness to reward. Thus, evidence of a significant increase in the strength of this bias from pre-treatment to post-treatment is suggestive of an improvement in reward sensitivity and a greater ability to modulate behavior as a function of reinforcement. Likewise, we observed that a greater response bias at pre-treatment was associated greater improvement in anhedonic symptoms. This finding mirrors those from prior studies showing that greater response bias at pre-treatment predicts response to eight weeks of pharmacotherapy (as clinically indicated) [36].

The current study had several limitations. Firstly, the small sample size, broad age range, and lack of control or placebo group limit conclusions regarding efficacy and generalizability. Although we did find that changes in neurocircuitry were associated with symptom change, there was not a main effect of time. Without placebo and non-treatment control groups, we are unable to distinguish between the specific pharmacological effects of ezogabine from non-specific factors. These non-specific factors may include patient expectation or natural variation in the depressive symptoms over time. Thus, we are unable to conclude if similar circuit changes would have been observed in the absence of drug treatment. To partially address the issue of the specificity of the observed effect of ezogabine, we conducted an analysis of changes in vCa circuitry associated with changes in depressive symptoms in a separate study of subjects who received a single infusion of ketamine as a treatment for MDD. This group demonstrated no association between changes in vCa connectivity and improvement in depression. While the inclusion of these results allows for a qualitative comparison to changes observed with ezogabine, caution is warranted in interpreting these results since these analyses do not represent a head-to-head comparison between the two treatments. In particular, subjects in the ketamine group were enrolled on the basis of having failed to respond to two or more adequate trials of an antidepressant medication and their course of treatment occurred on a different timescale. Additionally, we did not find any significant associations between VTA connectivity and clinical measures, which may have been due to a combination of our small sample size and the relatively poorer fMRI signal (and therefore smaller effects) of midbrain structures. As a separate potential limitation, it was unexpected that the vCa rather than the NAc was the mediator of the effects of ezogabine. Reduced signal strength in the region of the NAc may have prevented us from detecting a true effect. However, given that the vCa also receives dopaminergic innervation from the midbrain, which would be affected by KCNQ channel modulation, it is possible that the vCa is also an important mediator of ezogabine's antidepressant action. The striatum is organized as a series of spirals that proceed from a medial to lateral gradient, in which medial areas subserve limbic functions, central areas subserve cognitive functions, and lateral areas subserve motor functions [51]. The location of the vCa between medial and central areas implicates it in mediating between limbic and cognitive systems [52].

In conclusion, this is the first study investigating the antidepressant effect of the KCNQ-selective channel potentiator ezogabine in subjects with MDD. Ezogabine was associated with an improvement in depressive and anhedonic symptoms and exhibited good tolerability. Based on the findings of this preliminary study, future randomized controlled trials of ezogabine in depressive disorders are warranted. Understanding ezogabine's mechanism of action in the human brain could lead to additional novel treatments of depression focused on promoting active biological mechanisms of resilience, rather than reversing the pathological changes associated with the syndrome, which has dominated antidepressant drug discovery efforts to date. These resilience-enhancing or, 'active antidepressant' strategies may open up new avenues of drug discovery for mood disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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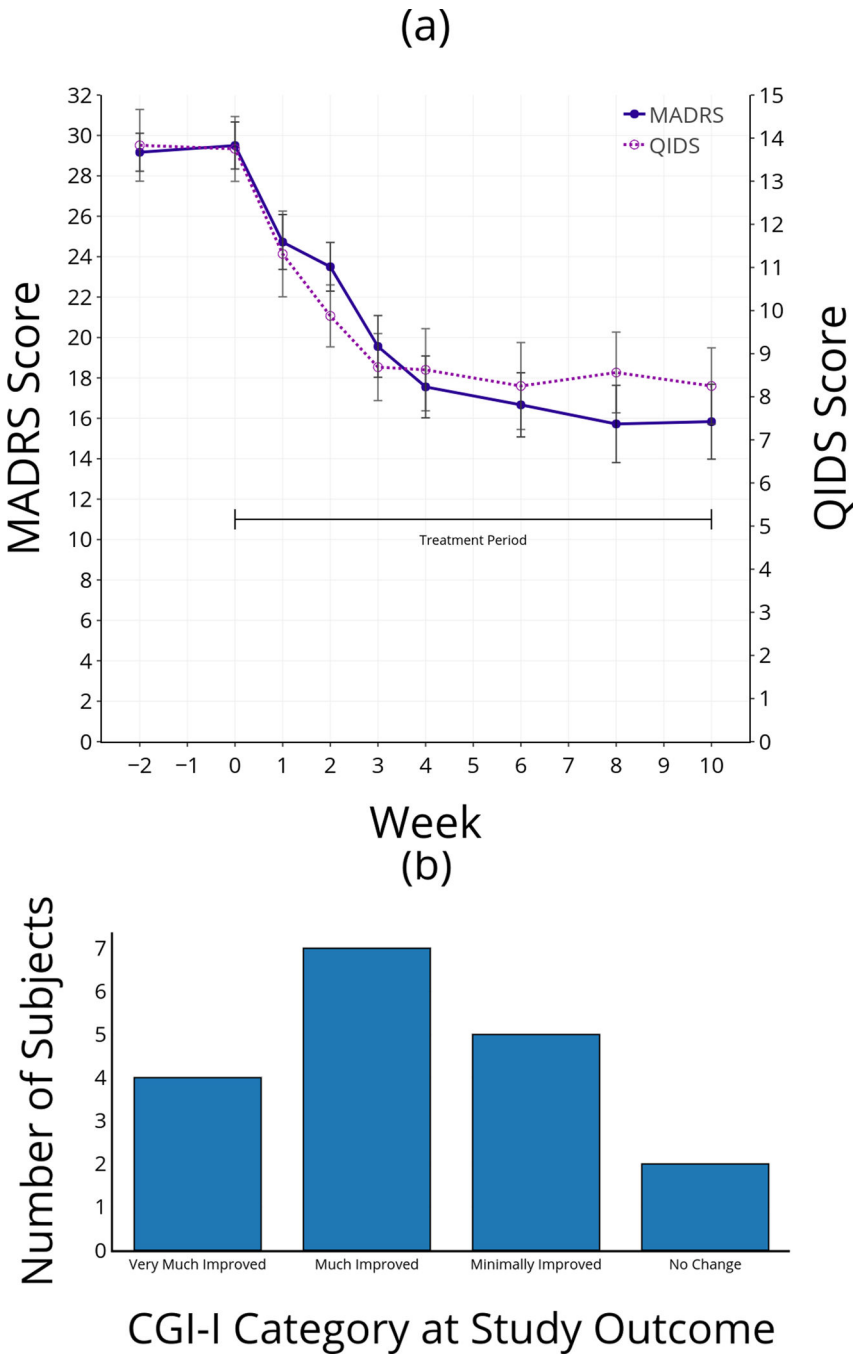

Figure 1. Change in Clinical Outcomes in Patients with Major Depressive Disorder Treated with the KCNQ Channel Opener Ezogabine.

(a) Mean MADRS and QIDS-SR score (± SEM) over time during course of ezogabine treatment. MADRS score decreased significantly from pre-treatment (week 0) to post-treatment (week 10) (mean change: −13.7±9.6, t_{17}=−6.01, p<0.001, Cohen's *d*=2.08) and throughout the study as a function of time (RM-ANOVA: $F_{3,52}$=21.96, p<0.001, partial-η^2=0.56). Likewise, QIDS-SR score was significantly reduced at study end compared to pre-treatment (mean change: −5.72±4.4, t_{17} =−5.53, p<0.001, Cohen's *d*=1.64). **(b)** CGI-I

category at study post-treatment. Eleven out of 18 (61%) of patients were classified as ‘much improved’ or ‘very much improved’ according to the CGI-I.

CGI-I, Clinical Global Impression—Improvement; MADRS, Montgomery-Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depression-Self Report.

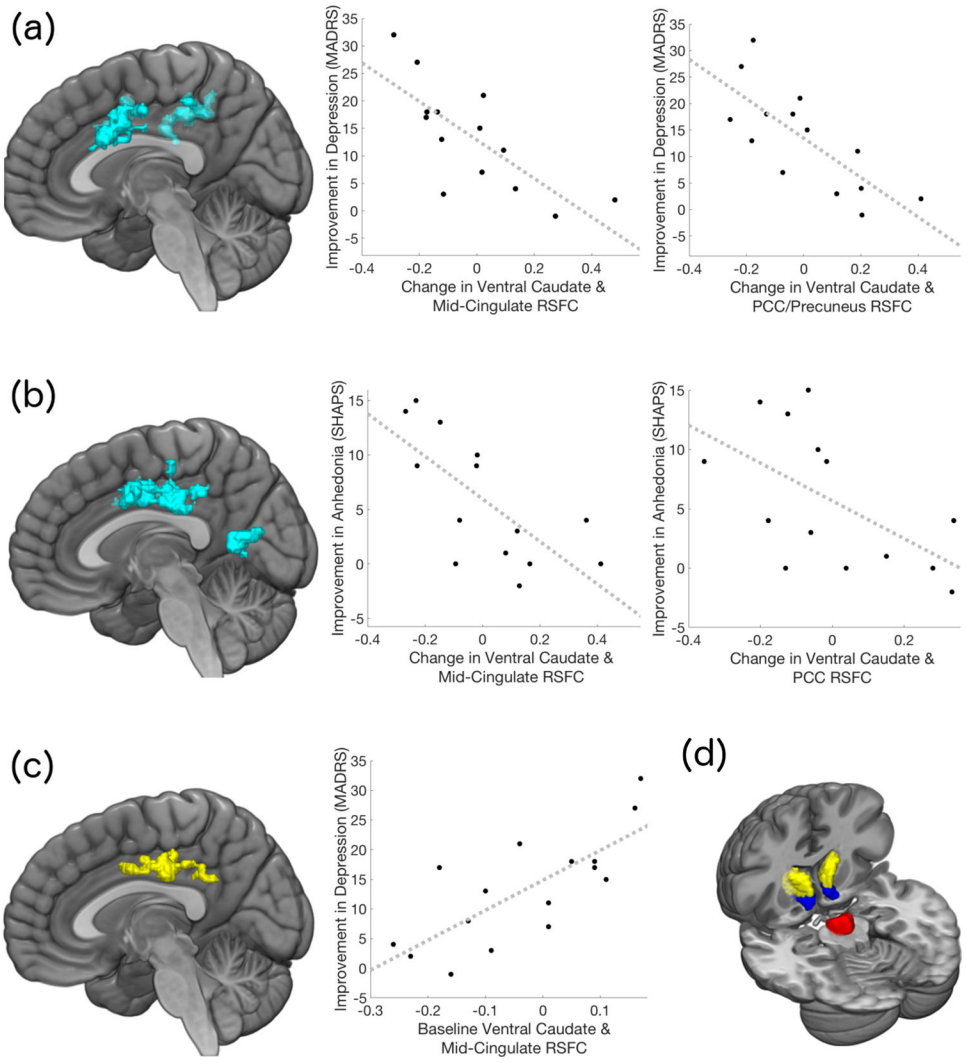

Figure 2. Functional Connectivity of the Ventral Caudate in Patients with Major Depressive Disorder Treated with the KCNQ Channel Opener Ezogabine.

(a) Clusters where reduction of RSFC with the vCa significantly correlated with reduction in MADRS score. (b) Clusters where reduction in RSFC with the vCa significantly correlated with reduction in SHAPS score. (c) Cluster where increased pre-treatment RSFC with the vCa significantly correlated with reduction in MADRS scores. (d) vCa, NAc, and VTA seeds, 3D view. Yellow: vCa, Blue: NAc, Red: VTA.

MADRS, Montgomery-Asberg Depression Rating Scale; NAc, nucleus accumbens; PCC, posterior cingulate cortex; RSFC, resting state functional connectivity; SHAPS, Snaith-Hamilton Pleasure Scale; vCa, ventral caudate; VTA, ventral tegmental area.

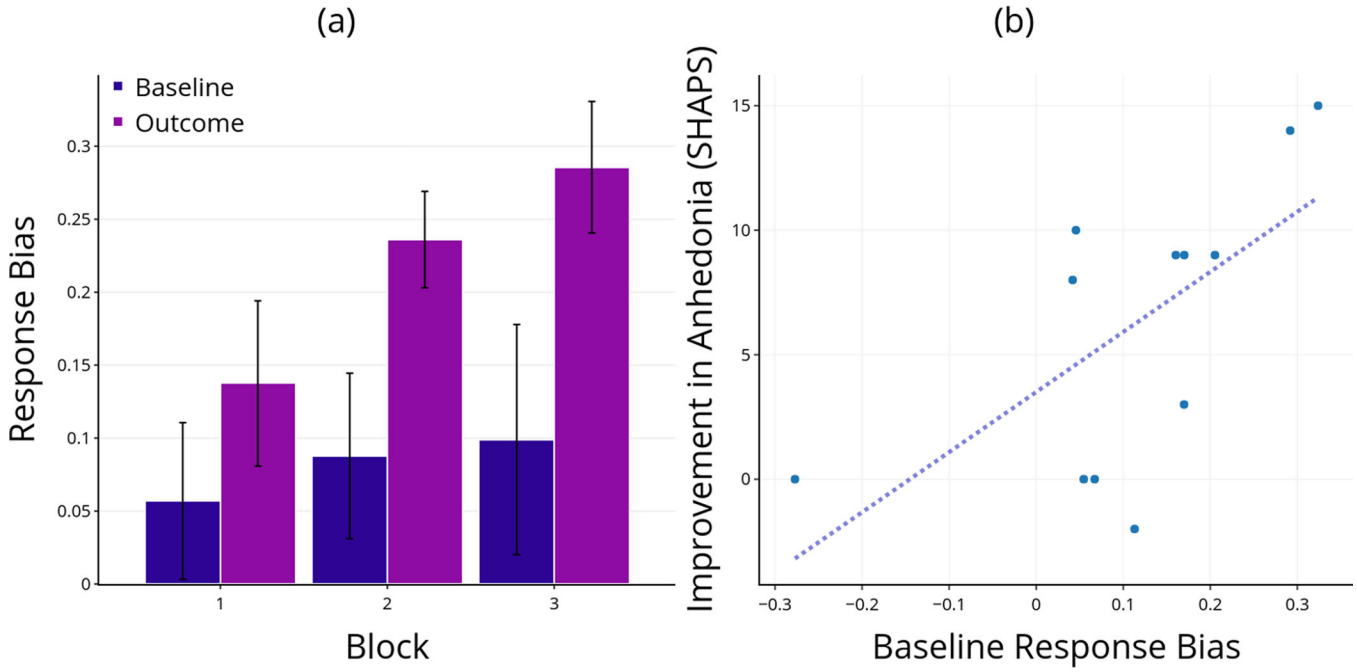

Figure 3. Change in Reward Learning and Association with Anhedonia in Patients with Major Depressive Disorder Treated with the KCNQ Channel Opener Ezogabine.

(a) Mean (± SEM) response bias across the three blocks of the PRT at pre-treatment and post-treatment. The main effect of block was significant due to a significant increase in response bias across blocks, indicating that the asymmetrical reinforcement ratio was successful at inducing a behavioral response bias ($F_{2,16=}5.38$, p=0.02, η^2=0.40). Furthermore, the main effect of time was significant due to a significant increase in overall response bias from pre-treatment to post-treatment, indicating that treatment improved the ability to modulate behavior based on prior reinforcement ($F_{1,8=}6.34$, p=0.04, η^2=0.44). (b) Higher pre-treatment response bias averaged across blocks 2 and 3 was associated with greater improvements in anhedonic symptom severity on the SHAPS following treatment (r=0.64, p=0.04).

SHAPS, Snaith-Hamilon Pleasure Scale.

Table 1.

Demographic and clinical characteristics of the sample (n = 18).

Demographic Characteristics	
Age, M (SD)	51.1 (9.1)
Male, n Male (%)	13 (72.2)
Race/Ethnicity, n (%)	
White/Caucasian	6 (33.3)
Black/African American	10 (55.5)
Hispanic/Latino	2 (11.1)
Employment, n (%)	
Full-Time	2 (11.1)
Part-Time	5 (27.8)
Retired	1 (5.6)
Unemployed	10 (55.6)
Educational Attainment, n (%)	
Not graduated from High School	1 (5.6)
High School	2 (11.1)
Some College (some college + 2 year college)	7 (38.9)
College	2 (11.1)
Some Graduate/Professional	2 (11.1)
Graduate/Professional	3 (16.7)
Relationship Status, n (%)	
Widowed	1 (5.6)
Divorced/Separated	5 (27.8)
Single, Never Married	12 (66.7)
Depression Characteristics	
Baseline QIDS-SR, M (SD)	13.8 (3.2)
Baseline MADRS, M (SD)	29.5 (4.9)
Number of Depressive Episodes, M (SD)	3.1 (2.2)
Age at First Depressive Episode, M (SD)	31.2 (16.5)
Current Depressive Episode	
Age at Onset, M (SD)	45.9 (10.1)
Duration in Months, M (SD)	61.4 (85.2)
Chronic Depression, n (%)	10 (55.6)
Recurrent Depression, n (%)	13 (72.2)
Psychiatric Characteristics	
Anxiety Disorder, n (%)	7 (38.9)
PTSD, n (%)	2 (11.1)
Past EtOH Use Disorder, n (%)	4 (22.2)

Abbreviations: EtOH, ethyl alcohol; MADRS, Montgomery–Åsberg Depression Rating Scale; PTSD, Post-Traumatic Stress Disorder; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report.

Table 2.

Additional outcome measures ($n = 18$).

Measure	Mean Change[a]	Standard Deviation	Statistic	p-value	Cohen's *d*
SHAPS	−6.06	5.34	$t_{17} = -4.81$	<0.001	1.00
TEPS-ANT	5.06	6.49	$t_{17} = 3.03$	0.004	0.50
TEPS-CON	5.28	7.58	$t_{17} = 2.96$	0.009	0.62
CGI-S	−1.56	1.25	$t_{17} = -5.29$	< 0.001	1.80
CGI-I	−1.72	0.96	$t_{17} = -7.62$	< 0.001	2.54
CD-RISC	8.22	12.16	$t_{17} = 2.87$	0.011	0.49

[a]Mean change = study end – baseline.

Abbreviations: CD-RISC, Connor-Davidson Resilience Scale; CGI-I/S, Clinical Global Impression – Improvement/Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology; SHAPS, Snaith-Hamilton Pleasure Scale; TEPS-ANT, Temporal Experience of Pleasure Scale – Anticipatory; TEPS-CON, Temporal Experience of Pleasure Scale – Consummatory.