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COMIRB Protocol

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Project Title: Reducing Hippocampal Hyperactivity and Improving Cognition in Schizophrenia

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I. Hypotheses and Specific Aims:

Schizophrenia is a leading cause of disability for Veterans. Among the symptoms of the illness, cognitive dysfunction remains the least well-treated (1). Consequently, much effort has been devoted to developing novel treatments for cognitive deficits in schizophrenia, using a variety of pharmacologic targets (2-4). Nonetheless, no compound has yet earned a federal indication for improved cognition in schizophrenia.

Using human functional imaging, studies have demonstrated that hyperactivity of the hippocampus may be a fundamental characteristic of schizophrenia. Namely, loss of hippocampal gray matter, as well as increased resting metabolism and neuronal activity are all observed (5-12). Recent work from our lab also has found hippocampal hyperactivity to be associated with poor cognition (12). As such, using hippocampal hyperactivity as a target biomarker may be a useful strategy for therapeutic development.

Two recent studies have found that low doses of the anti-epileptic drug levetiracetam (LEV) reduce hippocampal hyperactivity in patients with mild cognitive impairment (MCI), and that this effect correlates with improved performance on a memory task (13, 14). Unlike other anti-epileptic drugs, LEV also has pro-cognitive effects in patients with epilepsy (15-19), and improves cognition in mouse models of Alzheimer's disease (20, 21). Our lab also has recently shown that low-dose LEV improves hippocampal inhibitory function in a rodent model of schizophrenia (22). Compared to other anti-epileptic drugs, LEV is not significantly (<10%) protein bound upon administration, making it less likely to adversely interact with antipsychotic medication (23). Based on this evidence, the overall goal of this study is to test the hypothesis that LEV reduces hippocampal hyperactivity and improves cognition in schizophrenia.

II. **Background and Significance**: Despite the fact that the first antipsychotics were developed over 50 years ago, schizophrenia remains the most common debilitating mental illness for Veterans, due largely to the inability of antipsychotics to treat cognitive symptoms of the disease. Cognitive deficits more accurately predict quality of life in patients than positive symptoms, as illustrated by both cross-sectional (1, 24) and longitudinal (25, 26) reviews and are increasingly recognized as a core feature of schizophrenia. The deficits are not a side effect of antipsychotic medication, as they not only present in individuals with psychosis but also in at-risk populations that have not yet transitioned to psychosis (31-33). First-degree relatives of patients who do not meet diagnostic criteria for schizophrenia also often show deficits to a lesser degree, suggesting that cognitive symptoms have a genetic basis (34-37).

Although many schizophrenia clinical trials have included cognitive symptoms as an outcome measure, few studies have demonstrated positive effects. Most recently, the α7 nicotinic receptor partial agonist 3-(2,4-dimethoxybenzylidene) anabaseine (DMXB-A) improved scores on attention and working memory domains of a cognitive assessment battery (the MATRICS Consensus Cognitive Battery, MCCB) when the first treatment arms were compared, but not across all treatment arms (40). Another α7 agonist, Tropisetron, improved memory scores on another cognitive assessment battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (41). Behavioral therapies (e.g. cognitive remediation) have also shown promise in early stage trials (42). However, no compound has yet demonstrated efficacy in a large-scale (phase III) clinical trial. As such, additional mechanistically novel treatment strategies are urgently needed. One possible novel therapeutic target is hippocampal hyperactivity in schizophrenia.

As first observed by Liddle et al. (43), greater hippocampal regional cerebral blood flow (rCBF) in schizophrenia patients, relative to healthy comparison subjects, has been frequently reported (7-9, 44). Activity in the region has also been shown to correlate with the severity of psychotic symptoms (8, 43, 45). High-resolution measures of cerebral blood volume (8) and blood flow (46) have replicated and extended these findings. Furthermore, Schobel and colleagues have shown that basal blood volume in the hippocampus not only is greater in schizophrenia patients, but that the response predicts clinical progression to psychosis from a prodromal state (8, 9), suggesting that increased blood volume in the region is not a consequence of antipsychotic medication.

In addition to its target indications, LEV has a number of additional desirable pharmacologic, pharmacokinetic, and toxicological properties. Unlike many antiepileptic agents, LEV has a wide therapeutic index, with a large separation between the doses necessary to control seizures and those producing toxicity (Klitgaard et al., 1998). It has a very low potential for drug interactions, as it is not metabolized in the liver and is not significantly protein bound (<10%) (Patsalos and Sander, 1994; Perucca and Bialer, 1996); it is therefore unlikely to directly interact with antipsychotic medication. It is rapidly and almost completely (95%) absorbed following oral administration, with an oral bioavailability of close to 100% (Patsalos, 2000). LEV readily crosses the blood-brain barrier (Doheny et al., 1999; Tong and Patsalos, 2001). LEV is typically administered in twice-daily doses of 500-1500 mg for the treatment of epilepsy; these doses are generally well tolerated (Patsalos, 2000). Most relevant to the proposed study, LEV (62.5 -125 mg BID, two week administration) reduces hippocampal hyperactivity and improves cognition in patients with mild cognitive impairment (MCI) (Bakker et al., 2012).

In conclusion, based on previous studies showing efficacy in a clinical population and low toxicity, we hypothesize that LEV will reduce hippocampal hyperactivity and improve cognition in patients with schizophrenia, with a very low risk of side effects.

III. Preliminary Studies/Progress Report:

Previous studies from our laboratory have demonstrated that hippocampal hyperactivity can be pharmacologically reduced in schizophrenia. The majority of our previous neuroimaging work in schizophrenia has focused on the role of nicotinic agonists on the brain and behavior. We have studied the effects of these drugs in part due to their ability to normalize inhibitory hippocampal

circuitry due to deficits in nicotinic receptor expression on inhibitory interneurons (67). Specifically, we have demonstrated that acute administration of nicotine (4 – 6 mg gum) (68) as well as chronic (4 weeks) 150 mg b.i.d. administration of the α7 receptor partial agonist DMXB-A (69) reduces hippocampal hyperactivity in patients during SPEM. More recent work in our lab has demonstrated that nicotine and DMXB-A also reduce hippocampal hyperactivity at rest.

While it could be rightly argued that positive symptoms in schizophrenia have a more established relationship with hippocampal hyperactivity, and are a worthwhile treatment goal, a key motivation for this proposal is our recent discovery of a compelling relationship between hippocampal activity and cognitive symptoms, which, as outlined above, constitute a greater unmet treatment goal. We found a relationship between cognition, as measured by the MCCB, and resting state hippocampal activity, as part of the default network, in a cohort of 27 schizophrenia patients (12). A significant inverse correlation was observed between hippocampal activity and MCCB composite score ($R = -0.53$, $p = 0.004$). This effect was driven by effects on attention/vigilance ($R = -0.41$, $p = 0.031$), working memory ($R = -0.41$, $p = 0.031$) and visual learning ($R = -0.41$, $p = 0.032$). A significant positive correlation was observed with negative symptoms (total SANS score; $R = 0.42$, $p = 0.028$).

In conceptual agreement with the described relationship between hippocampal hyperactivity and cognition, a 4-week, 150 mg b.i.d. dose of DMXB-A (which reduced hyperactivity) improved performance on the verbal learning, attention, and working memory components of the MCCB, but only for the first arm of this clinical trial (40). The results were therefore inconclusive. Given this, while we still believe studying nicotinic agonism to be a promising research strategy, this proposal focuses on the same biological target, hippocampal hyperactivity, via a different mechanism. As described below, it is believed that if hippocampal hyperactivity could be more effectively targeted using the anti-epileptic drug levetiracetam (LEV), cognitive symptoms may be improved in schizophrenia.

A key motivating factor for this proposal was the observed effects of the drug levetiracetam in other patient populations. Levetiracetam [(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, Keppra, LEV] is an anti-epileptic drug whose primary clinical indication is for the treatment of partial and generalized tonic-clonic seizures (70). LEV is a broad-spectrum compound that may influence neural activity through a variety of mechanisms: 1) blockade of high-voltage-activated voltage-dependent Ca^{2+} channels to reduce neuronal depolarization in CA1 pyramidal neurons (71-73), 2) modulation of K^{+} channels to stabilize the membrane potential (74, 75), 3) enhancement of GABA- and glycine-gated currents to strengthen inhibitory tone (76), and 4) inhibition of presynaptic calcium channels to inhibit release of excitatory neurotransmitters into the synaptic cleft (77, 78). Interestingly, single nucleotide polymorphisms in genes that encode voltage-gated calcium channels, likely a primary mechanism of action for LEV, recently were associated with schizophrenia in the largest genome-wide association study to date (79). This result suggests that abnormal expression of these proteins may confer disease risk, possibly by influencing basal levels of neuronal activity.

Unlike other anti-epilepsy drugs, LEV improves cognition in epileptic patients (including language, memory, and executive function), contributing to its ability to improve their quality of life (15-19). Early studies have also shown promising effects of LEV on cognition in mouse models

of Alzheimer's disease (AD) (20, 21) and AD patients with epilepsy (80). LEV improves pattern recognition memory in patients with mild cognitive impairment (MCI) (13, 14).

Neurobiologically, low dose LEV reduces hippocampal hyperactivity both in rodent models of AD (20, 21) as well as in patients with MCI (13, 14). Motivated by this finding, we examined LEV effects in the DBA/2 mouse model of schizophrenia. The measure of hippocampal inhibitory function used was P20-N40 event-related potential (ERP) auditory gating, the mouse equivalent of the human P50 auditory gating paradigm, a widely used measure of human inhibitory neuronal function. Deficits in P50 gating (the ability of neuronal circuits to reduce early post-stimulus response to the second of a pair of identical, repeated clicks) are theorized to be due to dysfunction in inhibitory circuitry in the hippocampus, with drug effects on rodent gating being highly predictive of human effects (e.g. as with DMXB-A (81-83)). We found that a low LEV dose was associated with improved inhibitory gating (22). In summary, these preliminary data, along with prior reports of LEV effects on both hippocampal activity in different patient populations as well as its pro-cognitive effects in epilepsy, provide strong preliminary support for the proposal hypothesis.

IV. Research Methods

A. Outcome Measure(s):

Primary Endpoint

1) The effects of 4 weeks of LEV vs. placebo treatment on cognitive function (RBANS Total Scale score).

Secondary (Exploratory) Endpoints

1) The effects of 4 weeks of LEV vs. placebo on resting hippocampal activity.
2) Correlation between the effects of 4 weeks of LEV on cognitive function and the effects of LEV on resting hippocampal activity.
3) The effects of LEV vs. placebo on individual cognitive assessment domains (e.g. Attention).
4) The effects of LEV vs. placebo on clinical symptoms (BPRS/SANS/GAF/AIMS).
5) The effects of LEV vs. placebo on hippocampal CBF, measured by arterial spin labeling (ASL).
6) The effects of LEV on hippocampal and selective-attention-related neuronal activity.
7) The effects of LEV on hippocampal activity during a memory task (pattern separation).
8) Side effects and tolerability.
9) Treatment (drug or placebo) X smoking status (smoker or non-smoker) interaction effects.
10) The effects of LEV vs. placebo on eating behaviors (TFEQ/FCQ/PFS/VAS) will also be assessed as exploratory aims, given potential LEV effects on appetite (114).

B. Description of Population to be Enrolled

Subjects will be selected to be males and females 18 to 70 years old. We will include people who fulfill DMS-V criteria for schizophrenia or schizoaffective disorder. Participants will be excluded for current substance abuse, severe neurological disorders, head trauma/injury if

expected to affect MRI results, current prescription of LEV or a Non-vitamin K antangonist anticoagulant, if they are capable of pregnancy (i.e. pre-menopausal and not practicing at least one form of birth control), and for fMRI exclusion criteria (e.g., claustrophobia, weight>400lbs, metal in the body). Participants will also be excluded for recent psychiatric instability, as defined by a recent (< 2 months) change in antipsychotic medication and/or a recent (< 3 months) hospitalization for psychiatric symptoms. Both smoking and non-smoking subjects will be included. Subjects will have normal renal function, as assessed by a metabolic panel at screening if results current within one year are not already available. Subjects will be in generally good health as determined by a physical exam (blood pressure, pulse, cardiac, pulmonary, abdominal exam, neurological exam) at the time of screening or based on results from a physical exam within the last 6 months.

C. Study Design and Research Methods

A double-blind crossover design will be used. Participants will complete ~4 weeks of treatment with LEV 125 mg BID and ~4 weeks of treatment with placebo, with a ~4-week washout period between treatment arms. This ultra-low dose is well below the typical clinically used dose of 3,000 mg/day, which is generally well-tolerated. Participants and researchers working directly with them will be blind to treatment order (i.e., LEV/placebo or placebo/LEV). A statistician involved in the study will determine the treatment randomization scheme. Following phone screening, participants will complete an in-person screening day and 4 Study Days (Baseline Study Day, Post-Invention 1 Study Day, Post-Washout Study Day, Post-Intervention 2 Study Day). They will also complete a Check-In visit ~2 weeks into each 4-week treatment period. Patients with a confirmed diagnosis of schizophrenia or schizoaffective disorder will be targeted for recruitment. If needed, proper diagnosis will be confirmed using the Structured Clinical Interview for DSM-V Axis I Disorders (SCID), administered by trained personnel (study staff or a member of the Schizophrenia Research Center).

As part of COVID-19-related precautions, we may take a measure of the participant's temperature at the beginning of each visit to campus. If they have a fever greater than 100.4 °F, the participant will be advised to seek medical care and the visit will be rescheduled for a later time. If required by current VA/University guidelines, we will also use the most recent VA/University COVID-19 screening questions to screen for COVID-19 symptoms/risk in advance of their scheduled visit and upon their arrival to campus. If the participant endorses any symptoms, has been in unprotected contact (within 6 feet for > 30 minutes) or caring for someone who has been diagnosed with COVID-19 within the last 30 days without wearing proper PPE, or has had a diagnosis of COVID-19 in the last 30 days, the visit will be rescheduled for a later time. If they endorse symptoms of COVID-19, they will be advised to seek medical care. Additionally, we will follow VA/University guidelines regarding physical distancing and participant contact. Research staff and participants will be required to follow current VA/University guidelines regarding PPE (e.g., wearing masks, gloves, face shields when necessary). If the participant will be traveling to campus via public transportation or cab/rideshare, they will be instructed to follow current VA/University guidelines regarding PPE during transportation. Additionally, when possible, to minimize the number of in-person visits, some measures/visits will be conducted remotely, via phone or video call.

Screening Visit

The first study visit will include written informed consent and study screening. This visit will take place at either the VA Hospital, the UCD Clinical Translational Research Center (CTRC), Brain Imaging Center (BIC), and/or Schizophrenia Research Center, depending on what works best for participant convenience and scheduling. Measures may be administered remotely (via phone or video call) when possible. Screening measures will include a physical exam with a medical history review (or based on results from a physical exam within the last 6 months), measures of vital signs, a hearing test, demographics form, the Annett Handedness Questionnaire, the Fagerstrom Test for Nicotine Dependence, a smoking history questionnaire; a carbon monoxide breath test (to test for nicotine use; this may be omitted due to COVID-19 precautions), completion of an MRI screening form, the COVID-19 Impact Questionnaire, the Brief Psychiatric Rating Scale (BPRS), the Abnormal Involuntary Movement Scale (AIMS, completed if time allows and may also be repeated on future study days upon study doctor recommendation), the "Baseline" version of the Columbia Suicide Severity Rating Scale (C-SSRS), a blood sample (if results on renal function are not available within the last year), and a urine sample to test for substance use and pregnancy (if applicable). If a participant is unsure about the presence of metal in his/her body, an x-ray may be done to confirm appropriateness for MRI scanning. Blood samples will be taken by trained phlebotomists or nurses. If the blood sample is taken at the VA, it will be analyzed by the VA lab; if it is taken at the CTRC, it will be analyzed by the CTRC or UCH labs (as applicable for each test). Study research staff will perform the simple urine toxicology screen and pregnancy test. Subject payments will be in the form of agent cashier vouchers.

Baseline Study Day

If participants are deemed eligible for the study after the screening measures have been completed, they will be asked to come back approximately one week later for the Baseline Study Day. Subjects will arrive at the Anschutz Medical Campus (AMC; all Study Days will take place here because MRI scanning will be performed at the Brain Imaging Center, located on the Anschutz Medical Campus) in the morning in a fasted state (not having eaten for at least approximately 2 hours). Baseline Study Day procedures will include the following measures/assessments: side effects questionnaires, vital signs, weight, urine screen for substance use and/or pregnancy (if applicable), a carbon monoxide breath test (may be omitted due to COVID-19 precautions), concomitant medications form, AIMS (if recommended by the study physician, time permitting) clinical measures (BPRS, SANS, GAF, C-SSRS), food-related questionnaires (Three Factor Eating Questionnaire [TFEQ], Food Craving Questionnaire [FCQ], Power of Food Scale [PFS], Visual Analogue Scales of hunger, satiety, prospective food consumption [VAS]), and the RBANS cognitive test battery. A medical exam will only be completed on the Baseline Study Day if more than 60 days have elapsed since the screening visit and it is deemed necessary by the study physician. Participants will also complete an MRI scanning session, which will last approximately one hour. The MRI scan will include an anatomical MRI scan, a resting-state fMRI scan, and fMRI scanning during sensory/cognitive tasks. Soon after MRI scanning, participants will complete a post MRI questionnaire and will be given their first pill (LEV or placebo, depending on randomized treatment order). Approximately one hour after taking it, they will complete a second MRI scan. The purpose of this is to assess

acute response to treatment. The ~one-hour period approximately captures peak LEV absorption (Patsalos, 2000). After the second MRI, participants will be given breakfast.

Treatment Arm 1

After all Baseline Study Day procedures have been completed, participants will be given a ~2-week supply of either LEV (oral capsule) or placebo (oral capsule), depending on their treatment order assignment, with instructions to take the pills BID. Subjects will be given a pill log and written study instructions. Study staff will call participants within ~1 week after starting taking pills to administer a side effects questionnaire and the C-SSRS over the phone. ~2 weeks after starting the pills, participants will come in for a check-in visit (Check-in #1). This check-in visit will either take place at the VA or at the UCD CTRC, depending on what works best for participant convenience. During this visit, they will give their completed pill log to the researcher and the pill vial they were given (including any remaining pills that were not taken). Participants will complete a side effects questionnaire, clinical measures (BPRS, C-SSRS), and a concomitant medications form. They will also have their weight and vital signs measured. It would also be acceptable to administer this visit virtually via phone or video call, to minimize in-person visits. In this case, vital signs and weight measures may be omitted from this check-in visit, but all other measures would be administered virtually. At the end of this visit, participants will be given the next ~2-week supply of pills, to complete the ~4-week treatment period. If the visit is conducted virtually, a member of the research team may deliver the next ~2-week supply of pills to the participant and pick up the completed pill log. Participants will also be called by study staff during this next ~2-week period to assess side effects over the phone.

Post-Intervention 1 Study Day ("Study Day 1")

After the first ~4-week treatment arm has been completed (LEV or placebo, depending on randomized treatment order), participants will complete the Post-Intervention 1 Study Day ("Study Day 1"). This will include the same measures as the Baseline Study Day, described above. Additionally, participants will turn in their completed pill logs, their pill vial, and any remaining pills that were not taken. Unlike the Baseline Study Day, Study Day 1 (and the subsequent study days) will only include one MRI scanning session (lasting approximately one hour), rather than two MRI scanning sessions. On the morning of Study Day 1, participants should arrive in a fasted state (not having eaten for approximately 2 hours, same as the baseline day) and take their pill with research staff when they come in for their visit (i.e., they should not take it at home before coming in). The MRI scan will be timed to start approximately one hour after the participant takes their pill.

Washout Period and Post-Washout Study Day ("Study Day 2")

After Study Day 1, there will be a ~4-week washout period, during which participants will not take any pills. Participants will be called by study staff each week during this washout period to assess side effects. At the end of this washout period, they will come in for the Post-Washout Study Day (Study Day 2). The Post-Washout Study Day will include the same measures as completed in Study Day 1, but without pill administration prior to the MRI scanning session. Like the other study days, participants will come to the visit in a fasted state (not having eaten for at least approximately 2 hours).

Treatment Arm 2

At the end of the Post-Washout Study Day, participants will be given a ~2-week supply of pills (if they received LEV during the first treatment arm, they will now receive placebo and vice versa), with instructions to take the pills BID. They will also be given a pill log and written study instructions. As during the first treatment arm, study staff will call participants within ~1 week after starting the pills to administer a side effects questionnaire and the C-SSRS over the phone. ~2 weeks after starting the pills, participants will visit the lab for a check-in visit (Check-in #2). This check-in visit will either take place at the VA or at the UCD CTRC, depending on what works best for participant convenience. During this visit, they will give their completed pill log to the researcher and the pill vial they were given (including any remaining pills that were not taken). Participants will complete a side effects questionnaire, clinical measures (BPRS, C-SSRS), and a concomitant medications form. They will also have their weight and vital signs measured. It would also be acceptable to administer this visit virtually via phone or video call, to minimize in-person visits. In this case, vital signs and weight measures may be omitted from this check-in visit, but all other measures would be administered virtually. At the end of this visit, participants will be given the next ~2-week supply of pills, to complete the ~4-week treatment period. If the visit is conducted virtually, a member of the research team may deliver the next ~2-week supply of pills to the participant and pick up the completed pill log. Participants will also be called by study staff during this next ~2-week period to assess side effects over the phone.

Post-Intervention 2 Study Day ("Study Day 3")

After the second ~4-week treatment arm has been completed (LEV or placebo, depending on randomized treatment order), participants will complete the Post-Intervention 2 Study Day ("Study Day 3"). This will include the same measures as the Baseline Study Day, described above. Additionally, participants will turn in their completed pill logs, their pill vial, and any remaining pills that were not taken. On the morning of Study Day 3, participants should arrive in a fasted state (not having eaten for approximately 2 hours, same as the baseline day) and take their pill with research staff when they come in for their visit (i.e., they should not take it at home before coming in). The MRI scan will be timed to start approximately one hour after the participant takes their pill.

A table of study procedures is below:

Visit	**Cognitive Battery**	**Primary Neuronal Measure**	**Clinical Measures**	**Additional Measures**	**Compliance**	**Safety**
1: Screening			BPRS; AIMS; C-SSRS	Demographics; test for nicotine use/dependence; smoking history; CO breath test; handedness; weight; hearing test; COVID-19 impact		Written informed consent; physical exam; medical history; MRI screening form; concomitant meds; vital signs;

						urinalysis; blood draw
2: Baseline Study Day	RBANS	fMRI resting state (2 scans)	BPRS; SANS; GAF; AIMS; C-SSRS	fMRI sensory + cognition; anatomical MRI; food-related questionnaires (TFEQ; FCQ; PFS; VAS); weight; subjective improvement; CO breath test; Post MRI questionnaire	Pill pick-up	Physical exam; MRI screening form; concomitant meds; vital signs; urinalysis
3: Check-In			BPRS; C-SSRS	Weight	Pill log, pill count, and pill pick-up	Side effects; vital signs; concomitant meds
4: Study Day 1	RBANS	fMRI resting state	BPRS; SANS; GAF; AIMS; C-SSRS	fMRI sensory + cognition; anatomical MRI; food-related questionnaires (TFEQ; FCQ; PFS; VAS); weight; subjective improvement; CO breath test; Post MRI questionnaire	Pill log, pill count	Side effects; physical exam; MRI screening form; concomitant meds; vital signs; urinalysis
5: Study Day 2	RBANS	fMRI resting state	BPRS; SANS; GAF; AIMS; C-SSRS	fMRI sensory + cognition; anatomical MRI; food-related questionnaires (TFEQ; FCQ; PFS; VAS); weight; subjective improvement; CO breath test; Post MRI questionnaire	Pill pick-up	Side effects; physical exam; MRI screening form; concomitant meds; vital signs; urinalysis
6: Check-In			BPRS; C-SSRS	Weight	Pill log, pill count, and pill pick-up	Side effects; vital signs; concomitant meds
7: Study Day 3	RBANS	fMRI resting state	BPRS; SANS; GAF; AIMS; C-SSRS	fMRI sensory + cognition; anatomical MRI; food-related questionnaires (TFEQ; FCQ; PFS; VAS); weight; subjective improvement; CO breath test; COVID-19 impact; Post MRI questionnaire	Pill log, pill Count	Side effects; physical exam; MRI screening form; concomitant meds; vital signs; urinalysis

Possible Adverse Events

The investigators will record side effects weekly. Subjects will be asked each week to report dizziness, headache, nausea, hallucinations, paranoia, anxiety, depression, palpitations, urinary urgency, flatulence, peripheral sensations, and abdominal pain and other symptoms, as specified in the side effects questionnaire. If an adverse side effect deemed to be related to the drug is severe enough to require medical treatment, then the subject will be withdrawn. Their adverse side effects will be followed up with repeat medical and laboratory examinations, as clinically indicated, until the adverse side effect is resolved. A subject may voluntarily withdraw because of discomfort unrelated to the drug, such as dislike of the experimental protocol; these subjects will be replaced.

Safety issues that would lead to stopping the experiment are treatment-emergent vital signs in a medically compromised range (see subject stopping criteria) in any subject or drug-related side effects rated above moderate in two or more individuals.

Stopping criteria are as follows: An individual will be withdrawn by the investigator if there is a serious adverse event, including but not limited to severe weight loss, prolonged (more than a few days) insomnia, passing out, and severe agitation/hostility. Doses will not be administered in subsequent studies if they are found to produce an increase or decrease in pulse rate of 30% or above 110 beats per minute or an increase or decrease in blood pressure above 200/110 or below 90/60 mmHg. No rescue medications will be used.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Symptom Measures/Questionnaires

Description: Patients will be assessed for their current severity of clinical symptomology using the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), Global Assessment of Function (GAF), Abnormal Involuntary Movement Scale (AIMS), and the Columbia Suicide Severity Rating Scale (C-SSRS; baseline and "since last visit" versions). The BPRS is an interview that asks questions about somatic concerns, anxiety, guilt feelings, grandiosity, depressive mood, hostility, suspiciousness, hallucinations, and unusual thought content while observing the behavior, affect, and cognitive clarity of the subject. The SANS assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia and schizoaffective disorder. They are: affective blunting; alogia (impoverished thinking); avolition/apathy; anhedonia/asociality; and disturbance of attention. The GAF Scale is a 100-point scale that measures a patient's overall level of psychological, social, and occupational functioning on a hypothetical continuum. The AIMS records the occurrence of Tardive Dyskinesia (TD) in patients receiving neuroleptic medications and follows the severity of a patient's TD over time. Both versions of the C-SSRS are used for suicidal ideation assessment.

Risks: The questionnaires may cause fatigue, tiredness, and emotional discomfort. A previously unknown psychiatric disorder or symptom may be revealed during the interview. Should the subject request to be referred for further treatment for these newly discovered symptoms, the information will then become a part of the participant's medical record, and insurance companies will have access to this record, potentially affecting their ability to gain access to health or other insurance.

Justification: A staff member on the protocol who is blind to treatment status will administer all symptom measures. All of these symptom measures have been clinically validated in schizophrenia and schizoaffective disorder. The study subject may request to be referred for further evaluation and treatment. The discovery of new symptoms or disorders leads to the potential for better psychiatric treatment and care for the subject.

fMRI

Description: fMRI is technique that measures changes in local blood flow in the brain; these changes are associated with changes in local brain activity. Unlike other imaging techniques like Positron Emission Tomography, fMRI does not require injection of radioactivity substances. fMRI currently is the most widely used technique to study the functional anatomy of the human brain.

Risks: There are no known risks to the types of magnetic fields and radio waves that are used in functional MRI studies. However, some types of metal may be moved or may heat up by the magnets in the MR scanner. The MRI machine is a small round tube. Subjects with claustrophobia may feel uncomfortable. Very rarely, some people experience warmth and reddening of the skin. This usually goes away after a few minutes.

Justification: Currently, fMRI is the best method by which to functionally localize activity in the human brain. The safety risks associated with fMRI are minimal for subjects who are suitable to enter the scanner. fMRI is the most efficient and safest method to determine if the hypothesized biological target (lowering of hippocampal response) is achieved.

Discovery

Description: There is a risk of discovering an incidental finding or underlying abnormality in the brain during the MRI scans. Abnormalities and incidental MRI findings may include tumors, cysts, malformation, calcification, and atrophy.

Risks: If discovered, these findings could indicate the presence of harmful health issues. The subjects are informed during the consent process about this possibility, and also told that these scans, because they are not clinically diagnostic in nature, will not be examined for underlying abnormalities unless one is observed by chance. Should this occur, the subject would be referred to their primary care physician for further evaluation.

Justification: These abnormalities, if discovered, would provide the subject with an earlier detection than would have occurred otherwise. This earlier detection provides better longitudinal outcomes for the patient, should they choose to seek care from their primary care physician to whom they are referred.

Confidentiality

Description: Some things we cannot keep private. If the participant gives us any information about child abuse or neglect, we will report it to Social Services. If they indicate that they are going to

physically hurt someone or themselves, we will report that to the police. Also, if we are court ordered or subpoenaed to turn over study visit records, we have to hand them over to the court.

Risks: These situations present a risk of being identified as a research subject and, consequently, may lead to an association with a specific psychiatric diagnosis.

Justification: These laws and guidelines are in place to protect individuals from harm.

Blood Draw

Description: A blood draw, or venipuncture, occurs by placing a needle in a vein and letting the blood flow into a glass tube (~ 3 teaspoons). A lab then analyzes this blood to examine metabolic and renal function. Blood draws are a commonly used technique for ensuring subject health and safety before beginning study procedures.

Risks: The risks of venipuncture include excessive bleeding, fainting or light-headedness, hematoma, and infection. Using a phlebotomist with sufficient experience in hygiene practices and proper technique minimizes these risks.

Justification: The blood draw is necessary in order to ensure the subject is healthy enough to be enrolled in the study. The risks associated with a blood draw are far less than the risks associated with not gathering renal and metabolic function data and subsequently putting subjects in danger of renal damage. The risks of a blood draw are minimal, and most research participants are familiar with the procedure.

Repeatable Battery for the Assessment of Neuropsychological Status-Update (RBANS)

Description: The content of the RBANS consists of neurocognitive test paradigms that are well-validated. The subtests are described below:

Immediate Memory

List Learning: This consists of a list of 10 unrelated words, read for immediate recall over four trials, for a total maximum score of 40. The words are of moderate-high imagery and low age-of-acquisition, thereby reducing possible education effects on performance and easing translation.

Story Memory: This consists of a 12-item story, read for immediate recall over two trials, for a total maximum score of 24. Scoring is based upon verbatim recall, and the stories contained in the different forms of the RBANS follow the same basic structure.

Visuospatial/Constructional

Figure Copy: This consists of the direct copy of a complex geometrical figure, similar to the Rey-Osterrieth figure, but somewhat less demanding. There are 10 components of the figure, and

a structured simplified scoring guide (contained on the record form) yields a maximum score of 20. There is an additional detailed scoring guideline and associated transparency available as of 2008 to improve inter-rater reliability in scoring this subtest (this is the only subtest for which scoring is not entirely objective).

Line Orientation: Subjects are shown an array of 13 lines, fanning out from a common point of origin through 180 degrees. For each item, two target lines are shown beneath the array, and subjects must identify which lines they match within the array. There are 10 items, each containing two lines to be matched, for a total maximum score of 20.

Language

Picture Naming: This is a confrontation naming task, with 10 line drawings of objects that must be named by the subject.

Semantic Fluency: Subjects are given 60" to provide as many exemplars as they can from a given semantic category (e.g., fruits and vegetables).

Attention

Digit Span: This is a classic digit repetition test of working memory, with stimulus items increasing in length from 2 digits to 9 digits. Items are administering in order of length, and the test is discontinued after failure of two items at a given string length.

Coding: This processing speed subtest is very similar to the Digit Symbol subtest of the Wechsler scales. Subjects must fill in digits corresponding to shapes as quickly as they can on the basis of a coding key. After completing practice items, subjects have 90" to complete as many items as they can.

Delayed Memory

List Learning Free Recall: Free recall of the words from the initial List Learning subtest (max=10).
List Learning Recognition: Yes/No recognition for the words from List Learning, with 10 foils (max=20).

Story Memory Free Recall: Free recall of the story from the Story Memory subtest (max=12).

Figure Free Recall: Free recall of the Figure from the Figure Copy subtest (max=20).

Scoring: The raw scores from the subtests are scaled together to create index scores, and these are summed for conversion to a total scale score. The scaling tables are contained in the stimulus booklets, and computation of index scores requires less than 5 minutes.

Risks: There are no known risks for administering the RBANS.

Justification: The RBANS is simple to administer and is done so by trained personnel. The RBANS has been clinically validated and is a standard tool for assessing changes in cognition in clinical trials of schizophrenia (99). Study personnel have experience administering the RBANS, and it has been recently used in a published phase II clinical trial in schizophrenia by members of the study team (81).

Drug

The drug to be used in this study is (S)-α-ethyl-2-oxo-pyrrolidine acetamide (Levetiracetam, also known as Keppra). This drug is structurally similar to Piracetam, a synthetic derivative of the inhibitory neurotransmitter GABA. It can be administered orally and is typically prescribed for the management of seizures in doses from 500-1500 mg (31).

Risks: LEV is generally well tolerated at the lowest clinically-used of 3,000 mg/day. As such, using ultra-low dose of 125 mg BID is expected to be extremely well tolerated. The most common side effects are drowsiness, asthenia, and dizziness. More rare side effects are insomnia, anorexia, rhinitis, depression, nervousness, mood swings, ataxia, vertigo, amnesia anxiety, and hostility. LEV has no known drug interactions. Side effects will be monitored during the trial on a weekly basis. Stopping and subject withdrawal criteria are described in Study Design and Research Methods.

E. Potential Scientific Problems:

None.

F. Data Analysis Plan:

RBANS

The RBANS has a total scale score and 5 index scores. The scores are scaled with a mean of 100 and a standard deviation of 15. Comparisons (LEV vs. placebo) will be performed using mixed-effects, repeated measures models.

fMRI

The fMRI data will be preprocessed using fMRIPrep (Esteban et al., 2019). Condition effects (LEV vs. placebo) will be analyzed using mixed-effects, repeated measures models. Mean hippocampal BOLD response will be examined using an anatomically defined region of interest.

Clinical Symptoms

Effects of drug on BPRS, C-SSRS, SANS, GAF, and AIMS scores in patients will be evaluated using two-tailed paired t-tests. Effects of drug on total scores (e.g. total SANS, total BPRS) will be considered significant at a threshold of $p < 0.05$. Effects of drug on symptom subscales (e.g. SANS alogia) will be considered significant using a multiple comparisons-corrected threshold.

G. Summarize Knowledge to be Gained: We have hypothesized that hippocampal hyperactivity conferred through a loss of inhibitory tone may underlie sensory processing and cognitive deficits in schizophrenia and schizoaffective disorder. The proposed study will be the first to show that

LEV, a compound that reduces excitatory neurotransmitter release, may improve this phenotype in Veterans with schizophrenia and thereby improve cognition and normalize sensory processing abnormalities in the illness. If successful, these results will represent a novel baseline by which to measure the neurobiological and neuropsychological effects of novel therapeutic treatments.

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