

**Clinical Trial: Use of Clobazam in Treating Anxiety Comorbid with
Pediatric Epilepsy
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Abstract

Certain mood stabilizer/anticonvulsant medications may be better suited for epilepsy with comorbid psychiatric illness. Many anticonvulsants are broad-spectrum and are well established as improving outcome for epilepsy as well as for behavioral disorders. The intuitive choice for treatment in patients with such comorbidity would be medications with an established track record in successfully treating both conditions independently. Benzodiazepines are a mainstay of anxiety treatment as well as for epilepsy treatment.

Given its unique molecular structure, clobazam (Onfi[®]) is an example of a medication that theoretically could serve a “dual role” in terms of treating epilepsy as well as anxiety disorder. Anxiety is prominent in children and adolescents with epilepsy although the evidence base is underdeveloped.

This study would assess the utility of clobazam, which may represent a more effective and better tolerated treatment option for the numerous patients with seizure disorders who also have anxiety. This study is an investigator initiated proposal submitted by the PI and is a prospective open-label clinical trial of 20 children and adolescents with epilepsy. The assessments include standardized questionnaires widely used in clinical practice as well as structured psychiatric diagnostic tools. Overall, this study will contribute valuably to an understudied patient population and add key information to the evidence base that potentially will make an immediate clinical impact.

Overview of Study Design

This study is an open label, adjunctive, proof of concept, pilot clinical trial. Prospective participants will be identified from chronic epilepsy clinical populations of Johns Hopkins Hospital and Kennedy Krieger Institute. Pediatric participants will be considered for the study if neurologic status suggests the need for additional treatment, and behavioral characteristics are clinically significant. All participants will receive active treatment, involving flexible dose titration of clobazam and will be monitored for a period of four months. The study will be monitored and overseen by the Johns Hopkins Hospital Institutional Review Board.

Study Population

Prospective research participants will be identified from the chronic epilepsy clinic population of the Neurology Departments of Johns Hopkins Hospital and Kennedy Krieger Institute in addition to clinic populations recruited in the region. Pediatric participants will be recruited between the ages of 6 and 17 years, inclusive, in order to allow valid completion of behavioral measures. No exclusion will be made on the basis of gender or minority status.

Participants will be considered for the study if anxiety disorder symptoms appear to be prominent in children and adolescents with existing epilepsy. Subjects will be included in the study if they fulfill diagnostic criteria for an anxiety disorder with functional impairment.

Study Visits

After initial telephone contact and pre-screening is completed, the screening study visit will be scheduled. At that visit, study details will be reviewed and informed consent will be obtained by the PI. The screening study visit will include detailed medical and psychiatric history review, pertinent, physical examination (vital signs, neurologic exam), and assessment including semi-structured diagnostic interviews and rating scales.

Following the screening visit, participants who qualify and continue consent will enter into the active treatment phase of the study. The initial treatment phase will begin with a dispensing visit. It is expected that the dispensing visit may occur on the same day as the screening visit. However, if it does not occur on the day of the screening visit, it may occur within two weeks of the screening visit.

Continued contact with research participants will be done at regular intervals over a period of approximately 4 ½ months. In-person visits will occur biweekly for the first six weeks. In-person visits will occur monthly for the next two months. A total of seven in-person visits will occur including the baseline or screening visit. Participants who will continue on the drug, managed by their primary clinician, may have their care transitioned to their primary clinician before the time frame of the seventh in-person study visit.

At each contact, inquiry regarding adverse events, physical and mental health status, and compliance with treatment will take place. Safety assessment including mental health status and seizure diary review will take place at each subject contact. Safety assessment will include assessment of suicidal thoughts or actions. The PI will be involved with safety assessment at all study visits for each participant.

Telephone contacts will also be arranged at weeks 8, 12 and 16 to assess safety, adverse events and tolerability. Subject contact will occur every two weeks for the duration of the study.

All participants will receive adjunctive clobazam as active treatment. Initial titration will occur at standard dosage schedules, expected to be 5-10mg daily with 5-20mg biweekly increases. Increases may progress to a total of 40 mg daily, either in single dosages or divided dosages. Mimicking clinical practice, a flexible dose paradigm will be utilized to allow titration to effect and mitigation of

potential adverse events. Flexibility with minimum or maximum dosages will be employed in order to meet clinical needs.

Participants will be considered to have completed the study if they have successfully completed in-person visits. Participants will be free to withdraw from the study at any time by their choice, or if adverse events are intolerable or other risks outweigh potential benefits then participants will be terminated from the study. Participants who withdraw early for any reason will be assessed for safety, discharged from the study and returned to the care of their primary neurologist.

Inclusion criteria:

- Established diagnosis of epilepsy, characterized by focal seizures with suspected or documented localization in the temporal lobe. All participants will have active epilepsy that requires treatment with anticonvulsant medication.
 - Although it is not necessary to be seizure free, a seizure baseline period will be established in the 60 days prior to enrollment into the study.
 - Current regimen of anticonvulsant drugs must have been stable for 30 days prior to entry into the study.
- No episodes of seizure clusters or status epilepticus within 30 days prior to entry into the study.
- Established symptoms of anxiety with functional impairment.
- Baseline behavioral criteria for inclusion will include subscale scores above the norm for age and gender on one of the following:
 - Pediatric Anxiety Rating Scale (PARS).
 - Multidimensional Anxiety Scale (MASC)
- Male or female participants equal to or above age 6 and below age 18 at the start of the study. No exclusion will be made on the basis of gender or minority status.
- Good general health as determined by medical history and physical examination.
- Ability to swallow pills (participant will receive pill swallowing instruction if necessary). The medicine may be cut into pieces and/or mixed with applesauce.
- If female of childbearing age, a negative urine or serum pregnancy test must be established or assured at baseline. Additionally, the participant must agree to use abstinence or appropriate contraception methods or be otherwise incapable of pregnancy for the duration of the study. Pregnancy test results will be shared with parent or guardian. Pregnancy status (or prevention) and abstinence or contraception methods will be addressed

throughout the study for females of childbearing age as well as for post-pubertal males.

- Previous subjects who failed at any point to meet continuation criteria and withdrew early may be considered for re-enrollment by the PI on a case-by-case basis.
- Participant or legal caregiver capable of providing informed consent and fully capable of monitoring the subject's disease process and compliance with treatment.

Exclusion criteria:

- Previous allergic or hypersensitivity reactions to Onfi® or benzodiazepines
- Active substance abuse or dependence within 30 days of enrollment
- DSM-V diagnosis of psychotic illness or imminent risk of harm to self or others.
- Current use of antidepressants
- Current standing use of benzodiazepines (except as "rescue" medicine)
- Serious or unstable medical or neurologic conditions such as HIV, liver or kidney disease, cancer or diabetes.
- Participation in a previous experimental drug study within 30 days of baseline visit.
- Estimated IQ<70 as indicated by initial clinical assessment (rendering rating scales invalid)
- Insufficient capacity of caregiver or legal guardian to understand and appropriately consent for study procedures

Statistical Analysis Plan

Change from baseline will be analyzed statistically to test the main study hypotheses--that Onfi® has a dual role of improving both behavioral/psychiatric status, namely anxiety symptoms, as well as seizure control, in patients with epilepsy.

Outcome measures will encompass behavioral and neurologic status. The primary outcome variable will be Clinical Global Assessment of Functioning Improvement from baseline. CGI ratings will be attributed both to neurological status including seizure control, as well as behavioral status. CGI-Improvement ratings of a 1 or 2 (on a 7 point scale) will be considered positive responses. Paired student's t-tests will be used to compare baseline and study endpoint ratings for response versus non-response.

Secondary outcome measures will include changes from baseline in overall and subscale ratings of the Pediatric Anxiety Rating Scale (PARS), Multidimensional Anxiety Scale (MASC), and the Quality of Life in Epilepsy Scale. Positive outcomes will be defined as 10% score reduction or scores that drop below threshold of clinical significance. Paired student's t-tests will be used to compare baseline and study end outcomes for each measure.

Risks

The clearest risk is of potential side effects or other adverse effects of clobazam (Onfi®) drug treatment. Clobazam is a widely available anticonvulsant medicine with FDA indication for seizures associated with Lennox Gastaut Syndrome in pediatrics. All participants will have active epilepsy that requires treatment with anticonvulsant medication, so the risks incurred with drug treatment are equivalent to that experienced in typical neurologic clinical care for epilepsy. Close clinical monitoring and active side effect and adverse event monitoring at each contact will minimize risks due to drug side effect.

Specific risks notable for clobazam include rare but serious skin reactions, called Stevens-Johnson and toxic epidermal necrolysis. The skin reaction is very rare, but more likely to occur within the first 8 weeks of treatment or if clobazam is stopped and then restarted. Participants will be instructed to contact the 24 hour information line or emergency health care services for any occurrence of skin rash. In this circumstance, sudden stoppage of the medication is indicated.

Like other antiepileptic drugs, The U.S. Food and Drug Administration has reported that anticonvulsants including clobazam may increase the risk of suicidal thoughts or behaviors in a very small number of people taking the drug. Participants will be closely monitored for depression, suicidal thoughts or behavior, and unusual changes in mood or behavior. Psychiatric assessment will occur on each contact with participants to address this potential adverse reaction.

Clobazam may slow thinking and impair motor skills; so participants will be cautioned not to drive, operate heavy machinery, or engage in other dangerous activities until they know how the drug affects them. Given its structural similarity to other benzodiazepines, clobazam can also theoretically cause abuse and dependence. It has been categorized as a Schedule IV drug under the Controlled Substances Act, and thus should not be discontinued suddenly. Onfi should not be discontinued suddenly. Stopping clobazam suddenly can cause serious withdrawal problems, such as seizures that will not stop, hallucinations, shaking, nervousness, and stomach or muscle cramps.

Questions about medical and psychiatric history reveal private information, so there is a risk concerning confidentiality. The information gathered on the questionnaires will only be identified by a subject number and will be kept in a locked file cabinet in a locked office, or in a password protected computer.

Some questions might make children or parents think about things that are anxiety provoking or uncomfortable. In our experience, these reactions are mild and pass

very quickly. If a participant reports any problems or concerns about their behavior or mood, we will offer them information for further evaluation. We will report concerns to parents and treating physicians if concerns are significant.

Benefits

There is no guarantee of direct benefit. However, participants may reasonably expect to have improvement in seizure control and/or anxiety symptoms. Participation in the study may also contribute to a better understanding of the treatment effects of anxiety comorbid with epilepsy. Individual participants have reasonable potential to have improvement in their disease conditions as a result of participation in this study.

Participation in this study will also lead to increased knowledge base in the field and increased understanding of treatment options for children and adolescents with anxiety comorbid with pediatric epilepsy.

We will be happy to share results of standardized questionnaires, etc. with parents when the results are available. This may be very useful to subjects and their clinicians; however, we are clear to state that participation in this study should not be considered as a substitute for a formal mental health evaluation.

Payment and Remuneration

Study participants will not be paid for participating in this study.

Costs

There are no direct costs for participating in this study. Neither the patient, nor their insurance provider, will be charged for the costs of any of the procedures performed exclusively for the purpose of this research study. The patient and/or insurer will be billed for routine medical care services, or services not connected with the study. They will be responsible for any applicable copays, coinsurances and deductibles.

Routine clinical care will continue with the participants usual neurologists and primary care providers. If additional assessments including lab tests are necessary for clinical care purposes, these will be done outside of the context of this study.

Study medication will be provided to the participants at no charge for the duration of the study. Efforts will be made to continue treatment based upon clinical justification and in collaboration with the participant's clinical treatment team.

Parking is available free of charge to study participants at the facilities of Kennedy Krieger Institute.

Contractual Agreements

The study is funded by Lundbeck Pharmaceuticals based upon an investigator initiated proposal submitted by the principal investigator.

Confidentiality

Any information about the parent, child or their family obtained from this research will be kept as confidential (private) as possible. All records related to them or their child's involvement in this research study will be stored either in a password protected computer or in a locked file cabinet stored in a locked office. The patient's identity on these records will be indicated by a case number rather than by a name, and the information linking these case numbers with an identity will be kept separate from the research records. Neither the parent nor child will be identified by name in any publication of research results unless a separate form giving us their permission (release) is signed. Any data communicated to coordinating or collaborating sites will be fully de-identified, e.g. age in years, gender, etc., such that information cannot be personally linked to an individual subject.

Facilities and Equipment

This study will be conducted in the outpatient treatment facilities of the Departments of Psychiatry and Neurology at Kennedy Krieger Institute and Johns Hopkins Hospital.