Enhancing the Effects of Alcohol Treatment with Lamotrigine

Principal Investigator: Robert Miranda Jr., PhD, ABPP
ClinicalTrials.gov ID: NCT04770493
Date: February 02, 2021

Rationale

Alcohol use disorder (AUD) affects nearly one-third of adults in the United States during their lifetime. Excessive alcohol use causes myriad acute and long-term medical, psychological, and social problems. It carries an economic burden of $249 billion annually. Although advances in pharmacotherapy have improved treatment options for adults with AUD, treatment options for youth are limited.

Adolescent and young adult alcohol use is a leading public health concern. The harmful effects of underage drinking are irrefutable and include premature death and possibly irreversible damage to the developing brain. In addition, adolescence is a critical period in the pathogenesis of AUD; an estimated 3 to 15% of youth develop AUD before age 18. Clinical trials have tested psychosocial interventions with youth, including family treatments, cognitive behavior therapy (CBT), and motivational enhancement therapy (MET), that yield only modest short-term benefits. Our group has contributed substantially to this work.

One potential way to improve treatments is to augment psychosocial interventions with pharmacotherapy. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has mounted a concerted effort to identify medications that reduce drinking for nearly three decades. Although this effort improved treatment for adults, no medication is indicated for adolescent use, and randomized controlled trials with teenagers are almost nonexistent. This gap raises key questions about if and how medications could benefit youth. The urgency of this issue is underscored by the fact that optimizing treatment options for youth requires closing this critical gap.

Anticonvulsants are increasingly found to be efficacious for treating AUD. Many have intolerable side effects, however, that greatly limit their utility. Lamotrigine is a new generation mood-stabilizing anticonvulsant approved by the FDA to treat epilepsy in patients two and older and bipolar disorder in adults with fewer side effects than older anticonvulsants. We propose to study lamotrigine for three primary reasons.

- First, lamotrigine is safe and well tolerated by youth.
- Second, lamotrigine targets brain mechanisms implicated in the pathogenesis of AUD, namely the glutamatergic system, which mediates the acute and chronic effects of alcohol.
- Third, mounting human research that shows lamotrigine reduces alcohol and other substance use as well as craving.

On the whole, modulation of the glutamatergic system is a key pharmacological target for AUD treatment. Anticonvulsants reduce alcohol and other drug use in adults and adolescents but are not well tolerated. There is strong preclinical and emerging clinical

evidence that lamotrigine also reduces alcohol and other drug use, and human studies show it is well tolerated.

Objectives

The primary objectives of this study are twofold. The first primary objective is to evaluate the feasibility, acceptability, and tolerability of lamotrigine (25 mg/day to 200 mg/day in two divided doses) as compared to placebo for 9 weeks plus a psychosocial platform comprised of motivational enhancement therapy and cognitive behavioral therapy (MET-CBT; “Path 180”) among adolescents and young adults (ages 16 to 24 years) with AUD as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).

The second primary objective is to leverage a human laboratory paradigm to evaluate the effects of lamotrigine on an intermediate phenotype associated with alcohol use and outcomes in clinical trials. Specifically, we hypothesize that lamotrigine, as compared to placebo, will decrease alcohol cue-elicited craving in the human laboratory during in vivo alcohol cue reactivity.

Methodology

This proof-of-concept study is a double-blind, randomized, placebo-controlled, parallel group, single-site clinical trial. After obtaining consent/parent permission/assent, potential subjects and, if younger than 18 years, their parent(s) will complete a medical history and psychiatric diagnosis interview (about the adolescent) to screen for eligibility. Youth will also complete a physical examination, vital signs, drinking history and an alcohol breathalyzer test.

Forty-four eligible subjects will be randomized in an approximate 1:1 ratio to either lamotrigine or placebo for 9 weeks.

Dose titration, maintenance and taper will occur as scheduled below. Lamotrigine will be self-administered by subjects once daily after eating and with a full glass of water beginning on Study Week 1, Day 1 and continuing through Study Week 11, Day 7. The first dose will be taken in the study clinic whenever possible. Subjects will be provided with water and a snack to take with first dose. Dose will be titrated, as tolerated, to a target dose of 200 mg in two divided doses per day of lamotrigine. Following the target dose period, participants will complete a 2-week medication taper period (see dosing schedule below).Capsules should be swallowed whole and should not be cut, crushed, or chewed. Capsules should be taken with food and water.

Schedule of Administration of Investigational Product

Study Period	Time Period	Daily Dose	Dosing Schedule
Titration	Weeks 1-2	25 mg	Once daily
	Weeks 3-4	50 mg	Two divided doses
	Week 5	100 mg	Two divided doses
	Week 6	150 mg	Two divided doses
Maintenance	Week 7-9	200 mg	Two divided doses
Taper	Week 10	100 mg	Two divided doses
	Week 11	50 mg	Two divided doses

At the randomization/baseline visit and after 7 weeks of investigational product administration (i.e., Study Week 8), subjects will undergo a human laboratory paradigm (i.e., alcohol cue reactivity assessment).

Main Inclusion/Exclusion Criteria: Subjects will be male and female adolescents, ages 16 to 24 years old, who meet DSM-5 criteria for AUD. They must be seeking to reduce their alcohol use.

Investigational Product, Dosage and Mode of Administration: Lamotrigine (titrated for 6 weeks; target dose [200 mg/day/BID] for 3 weeks) will be over encapsulated and supplied by a contracted pharmacy, along with identical matching placebo capsules.

Reference Therapy, Dosage and Mode of Administration: Identically over encapsulated placebo tablets will be dispensed according to the same schedule as the lamotrigine capsules.

Statistical Analysis Plan

Primary Objectives

- Feasibility of retention will be determined by the percentage of enrolled subjects who complete the protocol (target ≥ 70%) and treatment-specific retention rates.

- Acceptability will be determined based on overall study withdrawal rates (≤ 20% considered acceptable), as well as treatment-specific withdrawal rates. Treatment satisfaction will be considered acceptable if ≥ 80% of responses on the CSQ-8 are rated

either “satisfactory” or “highly satisfactory.” We will also examine reasons for termination qualitatively.

Secondary Objectives

- We hypothesize that lamotrigine, as compared to placebo, will decrease alcohol craving during an alcohol cue-exposure paradigm in the human laboratory.