STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

Official title: Clinical Medication Development for Bipolar Disorder and Alcohol Use Disorders

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3. Research Strategy

3.1. Significance

3.1.a. Substance abuse is very common in persons with bipolar disorder (BPD) and schizoaffective disorder, bipolar type: BPD is a severe and persistent psychiatric illness affecting 1.3-3.5% of the population.[1-3] The prevalence of schizoaffective disorder is estimated to be between 0.5 and 0.8% of the general population.[4] Drug and alcohol abuse are common in BPD and Schizoaffective Disorder.[5, 6] Regier et al.[1] found a 61% lifetime prevalence of substance abuse in bipolar I and a 48% prevalence in bipolar II patients which is substantially greater than the 6% reported in the general population (Odds Ratio [OR] 8) and more than twice that of major depressive disorder (unipolar depression). Nesvag et al.[7] found a 19% five-year prevalence of substance use disorders in patients with schizoaffective disorder compared to the 2.4% population as a whole and 11% of patients with unipolar depression. ***Thus, patients with BPD, schizoaffective disorder, bipolar type and substance-related disorders represent a significant public health concern.***

3.1.b. Alcohol is a commonly abused substance in BPD and schizoaffective disorder, bipolar type: Kraepelin recognized the frequent occurrence of alcoholism in manic-depression over 100 years ago.[8] Since that time numerous studies have reported high rates of alcohol-related disorders in BPD.[9-11] In a community-based study, persons with bipolar I disorder had a 46% lifetime prevalence of alcohol-related disorders compared to 14% in the population as a whole (OR 5.5 for bipolar I and 3.1 for bipolar II).[1] BPD is also much more common in people with alcohol dependence than the general population, with a 6% prevalence in men (OR 12) and 7% in women (OR 5).[12] Alcohol is also problematic among individuals with schizoaffective disorder. A large-scale study compared substance use in individuals with chronic psychotic disorders (such as bipolar disorder with psychosis and schizoaffective disorder) to population control individuals. Results showed that 29% of individuals with schizoaffective disorder, bipolar type reported heavy alcohol use (>4 drinks/day) whereas only 8% of the control group reported heavy drinking.[13] Thus, patients with BPD or schizoaffective disorder represent an important subpopulation of alcohol-dependent persons.

3.1.c. Substance abuse has a negative impact on BPD and schizoaffective disorder, bipolar type: The negative impact of substance abuse on BPD is well documented. Studies report increased hospitalization[14-18] and lower rates of recovery during hospitalization, in patients with BPD and substance abuse.[19] Aggression and violence are also significantly greater in BPD and schizoaffective disorder patients with comorbid substance abuse.[20, 21] Substance abuse is also associated with medication non-adherence in BPD and schizoaffective disorder.[5, 22-26] Thus, substance-related disorders have substantial adverse impact on BPD and schizoaffective disorder.

3.1.d. Treatments for Alcohol Dependence: Several medications decrease alcohol use. Although disulfiram is effective for motivated patients, lack of adherence and safety concerns limit its use.[27-29] Acamprosate is an effective medication based on some,[30-32] but not all,[33] large randomized, controlled trials. Selective serotonin reuptake inhibitors (SSRIs) may decrease alcohol consumption in some persons.[34] Promising data on topiramate for alcohol dependence have been reported.[35, 36] Ondansetron may also reduce alcohol consumption.[37] The best-studied medication for alcohol dependence may be naltrexone.[38] Clinical trials generally support the efficacy of naltrexone in decreasing alcohol use.[39-46] However, negative studies have been reported,[47, 48] most notably a report in the VA system.[48] Meta-analyses have suggested modest effect sizes for both acamprosate and naltrexone.[49-51] Thus, the currently available pharmacotherapeutic options are not adequate, and new, innovative treatment approaches are badly needed. *Furthermore, atypical antipsychotics, a mainstay of BPD and schizoaffective disorder treatment, have generally been found to be ineffective in reducing alcohol use.[52] Thus, additional treatment options for people with BPD or schizoaffective disorder and alcohol dependence are badly needed.*

3.1.e. Limited data are available on medications for BPD and alcohol dependence: To date, only six randomized, controlled trials have examined the pharmacotherapy of BPD and alcohol dependence (Table 1). Drs. Brown and Salloum (PIs on the current application) were investigators on all but one of these studies. Salloum et al. reported that valproate was associated with a significant reduction in heavy drinking days in 59 patients with BPD and alcohol dependence.[53] Brown et al. reported reduction in depressive symptoms, but no significant between-group differences in alcohol use, in 115 outpatients with BPD and alcohol abuse or dependence given 12 weeks of quetiapine.[54] Brown et al. recently completed another trial of quetiapine in patients with BPD and alcohol dependence (n=90).[55] This sample had higher mean baseline alcohol

consumption than our earlier report. No between-group differences on any of the alcohol use measures were observed in the sample as a whole. However, a significantly greater reduction in drinks per heavy drinking day was observed with quetiapine in participants with greater than 90% medication adherence. Stedman et al. (Dr. Brown was an investigator on the study) also reported negative findings in a multisite study of quetiapine in BPD and alcohol dependence.[56] Brown et al. found no statistically significant reductions in alcohol use measures, alcohol craving, or liver enzymes with naltrexone as compared to placebo in 50 outpatients with BPD and alcohol dependence. [57] However, several alcohol use and craving measures showed trends and medium effect sizes favoring naltrexone. Tolliver et al. examined another standard alcohol use disorder treatment, acamprosate, in this population.[58] In this placebo-controlled trial (n=33) no statistically significant treatment differences were detected in drinking outcomes. However, a *post hoc* analysis revealed lower Clinical Global Impression scores of substance use severity in the acamprosate group at weeks 7-8. The above findings suggest that 1) alcohol dependence in BPD is challenging to treat and 2) more research and new approaches are needed. The current application is in response to an NIAAA PA that emphasizes the need for more research in the dual diagnosis population. The proposed study will help fill this knowledge gap.

We elected to include schizoaffective disorder (bipolar type) in addition to bipolar disorder due to the similarities in the symptom profile and due to the limited data available on pharmacotherapy for schizoaffective disorder and alcohol dependence. Schizoaffective disorder has poor diagnostic stability over time and genetic data does not support it being a distinct entity.[59] Thus, in many aspects it seems to be part of a spectrum that includes bipolar disorder with psychotic features. The treatment is also not different for schizoaffective disorder.

3.1.f. Promising new agents for treating alcohol use in BPD and schizoaffective disorder: We have conducted research on two agents (citicoline and pregnenolone) that, based on their mechanisms of action and preclinical and clinical data for mood or addiction, appear to be promising treatments for BPD/schizoaffective disorder and alcohol use disorders. Both are sold as over-the-counter supplements in the US. However, they have very different mechanisms of action.

Table 1. Placebo-Controlled Medication Trials in BPD and Alcohol Use Disorders

Authors	N	Medication	Design	Substance	Disorder	Findings
Salloum et al., 2005[53]	59	Valproic acid vs. placebo added to lithium	Randomized, placebo-controlled	Alcohol	Bipolar I	Decrease in alcohol use but no improvement in mood
Stedman et al., 2010[56]	362	Quetiapine vs. placebo	Randomized, placebo-controlled	Alcohol	Bipolar I	CGI, but no other outcomes, favored quetiapine
Brown et al., 2008[54]	115	Quetiapine vs. placebo	Randomized, placebo-controlled	Alcohol	Bipolar I and II	Quetiapine improved depressive symptoms but not alcohol use
Brown et al., 2009[57]	50	Naltrexone vs. placebo	Randomized, placebo-controlled	Alcohol	Bipolar I and II	Tends toward reductions in alcohol use and improved mood
Brown et al., 2014[55]	90	Quetiapine vs. placebo	Randomized, placebo-controlled	Alcohol	Bipolar I and II	No significant differences in alcohol use
Tolliver et al. 2012[58]	33	Acamprosate vs. placebo	Randomized, placebo-controlled	Alcohol	Bipolar I and II	No differences in alcohol use but positive effects on some secondary analyses

Proposed Study Drug 1 is Citicoline: ***What is citicoline?*** Cytidine-5'-diphosphocholine (a.k.a. citicoline) is marketed as a prescription drug in Europe and Japan and as a dietary supplement in the USA. Citicoline is produced endogenously from choline as an intermediate in the synthesis of cell membrane phospholipids. The citicoline molecule consists of cytosine, choline, ribose, and pyrophosphate and is rapidly metabolized to cytidine and choline after oral administration.[60] Cytidine is further metabolized to uridine, crosses the blood-brain barrier, and is converted to cytidine triphosphate (CTP). The free choline is phosphorylized into phosphocholine, which combines with CTP to reform citicoline.

How does citicoline work? Citicoline increases incorporation of phospholipids into membranes, enhances synthesis of structural phospholipids,[60] increases cerebral metabolism, increases norepinephrine levels in the cerebral cortex and hypothalamus, increases dopamine in the corpus striatum, increases serotonin in the cerebral cortex, striatum, and hypothalamus, and increases acetylcholine in the hippocampus and neocortex.[60-62] Finally, citicoline may also reduce brain glutamate activity by increasing expression of excitatory amino acid transporter-2.[63] Thus, citicoline works through a variety of mechanisms pertinent to alcohol dependence and mood disorders. While the possible involvement of cholinergic systems in alcohol use has been recognized for almost 40 years,[64] it has been a topic of relatively little attention. Thus, citicoline may offer a new approach to reducing alcohol use.

What is citicoline useful for? Citicoline is widely used for cognitive and neurological disorders in Europe. A Cochrane review concluded that citicoline was more effective than placebo for cognitive impairment with vascular dementia.[65] Citicoline may also decrease alcohol, cocaine and cannabis use. Nine studies have investigated the use of citicoline as a treatment for addictive diseases.

Small studies on citicoline have been published in cocaine dependence *without* comorbid BPD or Schizoaffective Disorder. For example, Renshaw et al.[66] demonstrated that cocaine users treated for 14 days with citicoline reported increased control over their cocaine use and decreased craving for cocaine. Licata et al.[67] conducted an eight-week double-blind, placebo-controlled study of citicoline (1000 mg/day) in 29 cocaine-dependent individuals. While citicoline did not significantly reduce cocaine use compared to placebo in this small study, a subgroup of participants with current alcohol use (n=24) taking citicoline demonstrated a significant (p=.02) reduction in days of alcohol use compared to placebo. Larger studies of citicoline for cocaine use have been conducted by the PI (Brown) in BPD and cocaine dependence. Brown et al.[68] conducted a 12-week, placebo-controlled, proof-of-concept study in 44 individuals with cocaine dependence and co-morbid BPD. Citicoline as add-on therapy (2,000 mg/day) was associated with 6.41 lower likelihood of a cocaine-positive urine at exit. Citicoline also improved declarative memory, impulsivity, attention and executive functioning performance. Completion rates were twice as great with citicoline as placebo. There was also a significantly *lower* total side effect burden with citicoline compared to placebo. In a subgroup of patients with alcohol dependence, citicoline was associated with decreases in alcohol use as well as substantial improvement in cognition (section 3.3.a.). A larger study (n=130) confirmed the reduction in cocaine use observed in this study (section 3.3.a.), *and also suggested a reduction in alcohol consumption.*

Brown & Gabrielson[69] conducted a double-blind, placebo-controlled trial of citicoline (2,000 mg/day) for bipolar and unipolar depression as well as methamphetamine dependence in 48 volunteers over 12 weeks. Participants receiving citicoline (n=28) had a significantly greater reduction in depressive symptoms, but not methamphetamine use, compared to placebo (n=20). Citicoline was safe and well tolerated and was also associated with significantly greater treatment retention and over twice the completion rates as placebo.

One study has specifically investigated citicoline in an alcohol dependent population. Chinchilla et al.[70] randomized 20 volunteers with alcohol dependence to citicoline or placebo. After 60 days the group receiving citicoline showed greater improvement than placebo on measures of attention, concentration and temporo-spatial orientation, and also had a 143 point decrease in gamma-glutamyltransferase (GGT) levels as compared to 38 points for the placebo group.

Why might citicoline be useful for BPD, schizoaffective disorder and alcohol dependence? **1) It may decrease alcohol use.** The literature discussed above suggests that citicoline was associated with a reduction in alcohol use in three studies (two subgroup analyses of those with cocaine dependence and one focusing on alcohol dependence). Citicoline appears to reduce alcohol even in studies where the change in cocaine use was not significant. Thus, citicoline may be more effective in reducing alcohol consumption than cocaine use. **2) Citicoline may improve mood.** One study of depressed dual diagnosis patients suggested citicoline may have antidepressant properties. None of the studies have suggested a worsening of depressive or manic symptoms with citicoline. **3) Citicoline may improve cognition in patients with BPD/schizoaffective disorder and alcohol dependence.** The severe and generally irreversible memory changes associated with the Wernicke-Korsakoff syndrome are a dramatic example of the effects of alcohol on cognition.[71] However, less severe, but still clinically significant, memory impairment is much more common.[72] BPD and schizoaffective disorders are associated with impairment in memory and executive functioning,[73, 74] even following resolution of mood symptoms.[75, 76] The combination of alcohol dependence and BPD appears to be associated with an additive detrimental effect on executive functioning and memory.[77-79] Citicoline might improve cognition in this dual diagnosis population. **4) Citicoline is very safe and well tolerated.** The extensive literature in neurology and the more limited literature in mood and addictive diseases suggest that citicoline has few side effects. It is very well tolerated and has no known drug-drug interactions. Thus, it seems

compatible as add-on therapy to existing medication regimens. **5) Citicoline may improve treatment adherence. It is critical to keep patients in treatment for addiction.** In two of our studies citicoline was associated with significantly better treatment retention than placebo.

Proposed Study Drug 2 is Pregnenolone: ***What is pregnenolone?*** Pregnenolone is a naturally occurring neurosteroid that is synthesized from cholesterol in the adrenal glands and also in the brain.[80, 81] Pregnenolone produces other neuroactive steroids.

How does pregnenolone work? Preclinical data suggest that pregnenolone acts on N-methyl-D-aspartic acid (NMDA) and gamma-amino butyric acid (GABA) receptors, and modulates hippocampal cholinergic systems.[82] Major metabolites of pregnenolone are the GABAergic neurosteroids, allopregnanolone and pregNANolone. Thus, pregnenolone modulates GABAergic systems through these metabolites. Pregnenolone also has effects on microtubules. A series of papers in *Proceeding of the National Academy of Sciences (PNAS)* demonstrated strong effects of pregnenolone on microtubule-associated proteins (MAPs). The MAP2 receptor has been identified as a receptor for pregnenolone and its synthetic analogue.[83] Pregnenolone binding to MAP2 is associated with a dose-dependent increase in tubulin assembly.[84]

What is pregnenolone useful for? Older studies suggested that pregnenolone improved irritability, insomnia, depression and anxiety.[85] More recent studies suggest that pregnenolone and its derivatives, such as allopregnanolone, have potential in treating neuropsychiatric disorders.[86-90] The combination of pregnenolone (30 mg/day) with didehydroepiandrosterone (DHEA) was more effective than placebo for positive symptoms and cognition in schizophrenia and schizoaffective disorder.[86] Another report in patients with schizophrenia or schizoaffective disorder suggested that pregnenolone (500 mg/day) reduced negative symptoms (e.g. anhedonia, affective blunting) of the illness.[89] Changes in Brief Assessment of Cognition in Schizophrenia (BACS) scores correlated with increases in pregnenolone levels.

A PI on the current application (Brown) has conducted two placebo-controlled trials of pregnenolone in patients with mood disorders with positive findings.[90] In the first study, 70 outpatients with unipolar or bipolar depression were given pregnenolone (100 mg/day) or placebo for eight weeks. The pregnenolone group showed greater improvement in depressive symptoms than the placebo group*. Furthermore, the data suggested a possible reduction in days of alcohol use (large effect size) with pregnenolone as compared to placebo in the subgroup of participants with an alcohol use disorder (section 3.3.a).* In the second study, 80 outpatients with bipolar depression were given pregnenolone (500 mg/day) or placebo for 12 weeks. The pregnenolone-treated group again showed significant improvement in depressive symptoms as compared to placebo. *Although alcohol and other substance use was, due to the exclusion criteria, uncommon in this study, much lower rates of alcohol use relapse were observed in those taking pregnenolone as compared to placebo (section 3.3.a.).*

Why might pregnenolone be useful for BPD, schizoaffective disorder, bipolar type and alcohol dependence? **1) Pregnenolone and other neurosteroids may decrease alcohol use.** Stress and alcohol administration are associated with increases in pregnenolone and some other neurosteroid levels, while acute alcohol intoxication is associated with elevated blood levels of allopregnanolone.[91] Early alcohol withdrawal is associated with low levels of allopregnanolone and pregnenolone that increase over four months of recovery. Chronic alcohol use is associated with blunted neurosteroid response to alcohol administration.[92] This finding suggests that exogenous pregnenolone administration might overcome the blunted neurosteroid response in alcohol use disorders and thereby decrease alcohol use and relapse. Pregnenolone, in a dose-dependent fashion, decreases alcohol self-administration in alcohol preferring rats without altering locomotor activity.[93] *A more recent study observed a significant reduction in alcohol intake and alcohol preference in rats acutely given pregnenolone (75 mg/kg).[94] The effect was weaker with chronic administration, although a significant reduction in alcohol intake was observed following eight days of pregnenolone administration.* These findings link pregnenolone administration to a reduction in alcohol intake. As will be discussed, preliminary findings by the PI (Brown) suggest pregnenolone may decrease alcohol use in outpatients with BPD (section 3.3.a.). As discussed above, pregnenolone may decrease alcohol consumption through at least two mechanisms. First, pregnenolone metabolites are potent modulators of a broad range of GABA receptors.[95] Other GABAergic medications such as gabapentin[96] and baclofen[97, 98] show promise for alcohol use disorders. In addition, chronic alcohol consumption is associated with impairment in microtubule formation and MAPS. Therefore, the effects of pregnenolone on microtubules are also pertinent to alcohol dependence. To our knowledge medications acting on microtubules have not been previously explored for alcohol use disorders. **2) Pregnenolone may improve mood.** George et al. found lower cerebrospinal fluid (CSF) pregnenolone levels in persons with bipolar or major depressive disorder than controls.[99] Pregnenolone levels were lower during

depressive episodes than euthymia. Low levels of pregnenolone compared to controls were also reported in generalized anxiety disorder and social phobia.[100, 101] A recent paper in *PNAS* reported that a synthetic analogue of pregnenolone that binds specifically to MAP2, had antidepressant effects comparable to standard antidepressants in the forced swim test.[83, 93, 102] In addition, this pregnenolone-analogue had more persistent effects than fluoxetine in the isolation-rearing model that induces depression-related behaviors such as memory deficits, anxiety, and increased passive coping. Because the social-isolation model is associated with increased alcohol use,[103] the findings suggest that pregnenolone may decrease alcohol use through actions on microtubules. Even more directly relevant to the current application are the data by the PI's group, discussed above, from two placebo-controlled trials by the PI (Brown) that suggest pregnenolone decreases depressive, and possibly manic, symptoms in patients with BPD (section 3.3.a.). **3) Pregnenolone may improve cognition.** As discussed above, cognition is frequently impaired in alcohol dependence and BPD or schizoaffective disorder. An older literature suggests cognitive enhancement with pregnenolone. The potential neuroprotective effects of pregnenolone through microtubules in alcohol dependence could be associated with improvement in cognition. Marx et al. found that elevations in pregnenolone in patients with schizophrenia or schizoaffective disorder following adjunctive pregnenolone treatment were correlated with cognitive improvements.[89]

Summary of the two proposed medications: We suggest that citicoline and pregnenolone are both promising medications for alcohol use*, as well as mood and cognition*, in BPD and schizoaffective disorder, bipolar type, which are well tolerated and appear to have positive effects on mood and alcohol use but work through different mechanisms. Therefore, both warrant further investigation.

Adaptive Clinical Trial Designs: As reviewed above, the BPD/schizoaffective disorder and alcohol use disorder combination is challenging to treat. A study design that facilitates development of better treatment approaches would be highly beneficial. The FDA Critical Path Initiative called on industry and researchers to develop innovative adaptive methods for making clinical trials more efficient and thereby less costly and time-consuming.[104] Adaptive designs can answer the same questions as traditional efficacy trials but with notable advantages in flexibility and efficiency (e.g. fewer participants) without loss of scientific rigor or credibility.[105] *Adaptive clinical trial designs are of much interest in many fields of medicine including drug abuse,[106] respiratory diseases, oncology, and stroke.[107]* Adaptive trial designs permit critical mid-trial design modifications, based on interim information, without undermining the validity and integrity of the trial. The proposed study lends itself to an adaptive drop-the-loser (DTL) design that permits evaluation of a range of treatment arms for evidence of clinical effect. As compared to standard design, *DTL provides for a decrease in expected treatment failures, while preserving the power of the study, and decreasing the number of people exposed to placebo.[108] Thus, the design is potentially safer, faster, less expensive and more efficient than traditional designs.* Using this design, both treatments in the proposed study will be compared to placebo using a three-arm, randomized, double-blind design. An interim analysis plan, conducted after 50% of participants have been enrolled, will apply predetermined decision rules for dropping a treatment condition that fails to show clinically meaningful efficacy over placebo. This adaptive "pruning" permits randomization of remaining participants to a condition that demonstrates the most encouraging performance. Thus, the proposed design allows for assessment of multiple medications, as well as an adequately powered trial of the most promising one, in a single trial, an approach that is efficient both in time and resources. In addition, this design is consistent with an objective of the NIAAA PA the application is in response to, which highlights development and implementation of adaptive clinical trial designs in alcoholism clinical research.

3.2. Innovation

Alcohol dependence is very common in BPD and schizoaffective disorder. However, literature on the treatment of these dual-diagnosis populations is quite limited. Thus, the patient population studied is innovative. The drugs tested are also innovative. Each is a dietary supplement with interesting clinical and preclinical properties. In addition, the two treatment options have different mechanisms of action that are relevant to alcohol use disorders and BPD/schizoaffective disorder but have not been the focus of extensive attention. Thus, the proposal is consistent with the NIAAA goal to "Discover, develop, and test new, more effective agents to prevent or reduce drinking" (NOT-AA-14-008). The 2-site clinical adaptive trial design is innovative. Adaptive designs are widely used in some areas of medicine, and are currently being explored in the drug abuse field,[106] but, to our knowledge, have not been used in alcohol research. The design allows for the testing of two treatments as well as an adequately powered trial of the more promising option. The stopping rules are also innovative. If neither of the treatments appears promising, the trial will be stopped. This approach decreases the investment of time and resources should the treatments appear to not be very

effective. If an option is promising then the timeframe for drug development will be faster than with current approaches. We suggest that this approach is consistent with the objective of NIAAA to conduct more efficient clinical trials with novel methodology,[109] and with the specific PA. *Finally, we include an exploratory analysis that will examine, with both medications, whether changes in alcohol use occur before or after changes in alcohol craving, mood or cognition. To our knowledge, such an analysis has not been reported in dual BPD/schizoaffective disorder and alcohol use clinical trials. The findings will help inform whether the effects of the medications on alcohol use are driven by improvement in craving and other clinical outcomes.*

Summary: Preclinical and clinical data as well as mechanistic justification have been presented suggesting citicoline and pregnenolone are each promising treatments for alcohol use in BPD and schizoaffective disorder, bipolar type. *Both appear to have favorable side effect profiles and no known drug-drug interactions. Thus, they have the potential to be safely used in a dual diagnosis population already taking other medications.* A clinical trial of both supplements is proposed. The findings will inform treatment in BPD/schizoaffective disorder and alcohol use disorders, and may lead to further study in a broader alcohol use disorder population, as well as in patients with mood disorders.

3.3. Approach

3.3.a. Preliminary Studies: The investigative team has extensive experience conducting clinical trials in this dual diagnosis population. Staff members at both sites have extensive experience conducting research in this population. Four studies directly pertinent to the current proposal are discussed below.

Pilot Study 1: A 12-week randomized, placebo-controlled, add-on, trial of citicoline
Methods: 44 outpatients with BPD and cocaine dependence were randomized to citicoline (2000 mg/day) or placebo.
Results: Those who took placebo had 6.41 times greater odds of testing positive for cocaine at exit than those who took citicoline. Days of cocaine use decreased with citicoline treatment, but increased with placebo (Cohen's *d*=0.6, medium effect size). The citicoline group had significantly (p = 0.006) better performance on the Rey Auditory Verbal Learning Test (RAVLT), an alternative word list (declarative memory). The Stroop Color test (executive functioning, attention, impulsivity) showed greater improvement with citicoline than placebo (2.8 ± 7.4 vs. -1.1 ± 4.6, p=0.04, Cohen's *d*=0.6). Study completion rates were over twice as high with citicoline as placebo. Side effects scale scores were significantly lower with citicoline than placebo (8.9 ±1.5 vs. 9.8 ± 1.5, p<0.001).

Among participants with alcohol use disorder (in addition to cocaine), and active alcohol use at baseline (n=14), potentially meaningful changes in alcohol use and craving were observed. Citicoline-treated patients had a significant decrease in alcohol craving based on a 0-100 mm visual analogue scale (-28.7±31.3, p=0.05) while the placebo-treated group showed a much smaller decrease in alcohol craving (-1.9±66.4, p=ns). Despite modest baseline values, alcohol use decreased by 0.9±1.4 days/week in the citicoline group as compared to only 0.4±0.9 days/week with placebo. Heavy drinking days decreased by 0.9±2.1 (p=0.04) days with citicoline as compared to 0.0±0.6 with placebo. Drinks per drinking day decreased by 2.4±11.3 with citicoline and 0.8±2.6 with placebo. In the alcohol use group, RAVLT delayed recall performance increased by 12.4±12.9 points with citicoline (p=0.04), but decreased by 1.8±3.5points with placebo (Cohen's d = 1.5, large effect size).
Significance: Findings suggest reductions in both cocaine and alcohol use with citicoline. Memory improved with citicoline, particularly in those with alcohol use. Citicoline was safe and well tolerated, and was associated with better study retention than placebo.

Pilot Study 2: A 12-week, double-blind, placebo-controlled trial of citicoline add-on therapy in patients with BPD I disorder and cocaine abuse/dependence
Methods: 130 outpatients with BPD (depressed), cocaine dependence and a cocaine-positive urine at baseline were given citicoline or placebo add-on therapy to stable doses of mood stabilizers. Both groups received cognitive behavioral therapy and a contingency management plan of escalating payments for each urine sample provided. These payments were not related to whether the urine drug screen (UDS) was positive.
Results: Among those with at least one post-baseline visit (n=60 citicoline, n=61 placebo) a group (f=4.5, df=1,1057, p=.0351) and group by time interaction (f=11.2, df=1,1057, p=.0009) was observed. Similar results were observed when imputing missing data as cocaine-positive [treatment group effect (p=.0222), treatment group by time effect (p=.0151)]. Completion rates non-significantly favored citicoline (71% vs. 57%).

In those with alcohol dependence, citicoline (n=33) showed a trend toward a greater decrease in days per week of alcohol use than placebo (n=37) (-3.67±4.11 days vs. -1.86±4.44 days, p=.084).

Significance: The study highlights our research experience with citicoline and in conducting large studies in patients with BPD and substance use disorders. The results confirm the reduction in cocaine use with citicoline we observed in Pilot study 1. *Although very preliminary in nature, the data also suggest that citicoline was associated with almost twice as greater decrease in days of alcohol use than placebo.*

Pilot 3: Placebo-controlled trial of pregnenolone (100 mg) for MDD or BPD depression
Methods: 70 participants with BPD or recurrent MDD and history of substance abuse/dependence received pregnenolone (100 mg/day) or placebo for 8 weeks. Participants were assessed using the Hamilton Rating Scale for Depression (HRSD), and Young Mania Rating Scale (YMRS).
Results: The pregnenolone group showed trends toward greater improvement, relative to placebo, on the HRSD and YMRS. Study completers demonstrated a statistically significant reduction in HRSD scores with pregnenolone as compared to placebo. Side effects were similar to placebo. Active substance use was uncommon. *A total of 11 participants in each group had a history of alcohol use disorders with three in each group reporting some alcohol use at study exit. In the pregnenolone group, these participants reported only 1.0±0.0 days of alcohol use in the prior two weeks compared to 2.7±1.2 days in the placebo group (Cohen's d =2.0, large effect size). Pregnenolone appeared to be safe and well tolerated in participants with alcohol use. A total of 11% with active alcohol use reported an adverse event (not study related) while receiving pregnenolone compared to 10% without alcohol use.*
Significance: The data suggest that pregnenolone is well tolerated and improved depressive symptoms. Few participants had current alcohol use, but the findings are *suggestive of* less alcohol use with pregnenolone.

Pilot Study 4: Placebo-controlled trial of pregnenolone (500 mg) for bipolar depression
Method: Adults (n=80) with BPD, depressed mood state, were randomized to pregnenolone (500 mg/day) or placebo, add-on therapy, for 12 weeks. Outcomes included the HRSD, Inventory of Depressive Symptomatology – Self-Report (IDS-SR), Hamilton Rating Scale for Anxiety (HRSA) and YMRS. Serum neurosteroid levels were assessed at baseline and week 12. Participants with active substance use disorders were excluded.
Results: In participants with at least one post-baseline visit (n=73), a significant group by visit effect for the HRSD was observed (f=2.61, p=0.025). Depression remission rates were greater in the pregnenolone group (61%) compared to the placebo group (37%), as assessed by the IDS-SR ($\chi 2(1)=3.99$, p=.046). Significant baseline to exit changes in pregnenolone, allopregnanolone and pregNANolone levels were observed in the pregnenolone group but not in the placebo group. In the pregnenolone group, baseline to exit change in the HRSA correlated negatively with changes in allopregnanolone (r=-0.43, p=.036) and pregNANolone (r=-0.48, p=.019) levels. Pregnenolone was well tolerated. Side effects and retention were similar in the two groups.
Due to inclusion and exclusion criteria, people with current active AUD were excluded. However, a total of n=5 for pregnenolone and n=8 for placebo with a history of AUD were enrolled. Among these participants, 50% in the placebo group relapsed to alcohol use during the study as compared to only 28% in the pregnenolone group.
Significance: The data, when combined with our prior pilot study, suggest that pregnenolone decreases depressive symptom severity in BPD. Pregnenolone therapy was associated with significant increases in the GABAergic neurosteroids pregNANolone and allopregnanolone that correlated with improvement in anxiety. We have previously reported extraordinarily high rates of anxiety disorders (e.g. 57% generalized anxiety disorder, 54% panic disorder) in BPD and alcohol dependence.[110] *Although, few participants had alcohol use disorders, the data suggest lower relapse rate with pregnenolone than with placebo.* Thus, relationships between improvement in anxiety and increases in neurosteroid levels may be clinically important in this dual diagnosis population.

3.3.b. Experimental Study Overview: A 12-week, randomized, double-blind, parallel-group, placebo-controlled adaptive design study of citicoline and pregnenolone is proposed in 199 persons with alcohol use disorder and bipolar I or II disorder or schizoaffective disorder, bipolar type. The primary aim will be to assess change in alcohol use (drinks per drinking day-primary outcome measure) by the Timeline Followback (TLFB) method.[111, 112] Biomarkers of alcohol use, alcohol craving, mood and cognition will also be assessed. Relationships between neurosteroid and choline levels and the outcome measures will be explored.

3.3.b.1. Details of Proposed Experiment: A 12-week, randomized, double-blind, parallel-group, placebo-controlled adaptive, DTL design clinical trial of citicoline and pregnenolone will be conducted in 199 outpatients with bipolar I or II disorder or schizoaffective disorder, bipolar type and current alcohol use disorder. Potential participants will be identified through physician referral, flyers, and brochures at clinics that treat the population needed for this study. In most cases the potential participant will call our clinic. At this time an appointment will be arranged, informed consent will be obtained, and assessment procedures, including a review of inclusion and exclusion criteria, will be performed.

A structured clinical interview for DSM-5 (SCID)[113] will be performed to establish the diagnoses of bipolar I or II disorder or schizoaffective disorder, bipolar type and alcohol use disorder. Clinical Institute Withdrawal Assessment of Alcohol Use-Revised (CIWA-Ar)[114] will be administered. Eligible participants will then be given the $HRSD_{17}$,[115] $IDS\text{-}SR_{30}$,[116-119] YMRS,[120] HRSA,[121] Penn Alcohol Craving Scale[122] (PACS), Short Index of Problems (SIP), and a urine drug screen. Safety and side effects will be assessed with the Systematic Assessment for Treatment Emergent Events (SAFTEE).[123] Recent alcohol use (and, if present, other substance use) will be assessed using the Timeline Followback (TLFB) method. Length of problem alcohol use will be assessed by asking "When did alcohol first start causing you problems?" Blood will be drawn for laboratory analyses including a complete blood count (CBC) and Comprehensive Metabolic Panel (includes a liver panel with AST, ALT as well as lipids and electrolytes), and GGT and carbohydrate-deficient transferrin (CDT) will be added at baseline (week 0) and weeks 6 and 12. Cognition, including the domains of memory, decision making, impulsivity, attention, and executive functioning will also be assessed at baseline and week 12. A physical examination will be performed and weight obtained. Women of childbearing potential will receive a urine pregnancy test at baseline, week 6, and week 12 and will be counseled about effective contraceptive methods. A psychiatrist (PI or Co-I) will assess participants at baseline and weekly follow-up visits and will participate in the informed consent process. The psychiatrist will also prescribe a mood stabilizer (Lithium Carbonate or Risperidone) if the participant is not already on a stable dose. If prescribed, Lithium will be started at 600 mg nightly and Risperidone will be started at 2 mg nightly and continued for 21 days prior to starting the study medication or placebo. Mood stabilizer levels will also be tested, per clinician judgement, to assure the participant's medication adherence. The active medication or placebo capsules will be initiated at baseline and increased weekly in weeks 1, 2 and 3 to achieve the target doses for citicoline (2000 mg/day) or pregnenolone (500 mg/day). The titration schedule is as follows:

Pregnenolone

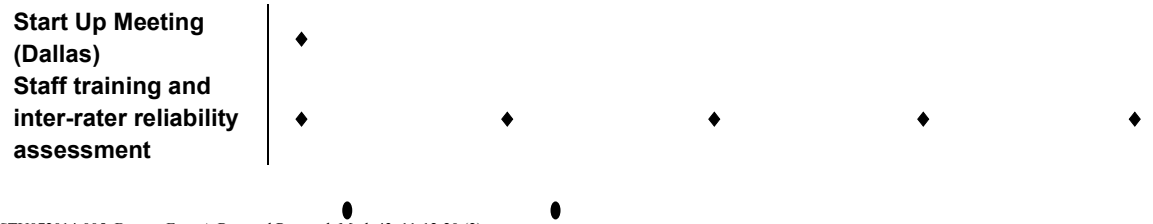
Week 0	50mg BID
Week 1	100mg BID
Week 2	150mg BID
Weeks 3-12	250mg BID

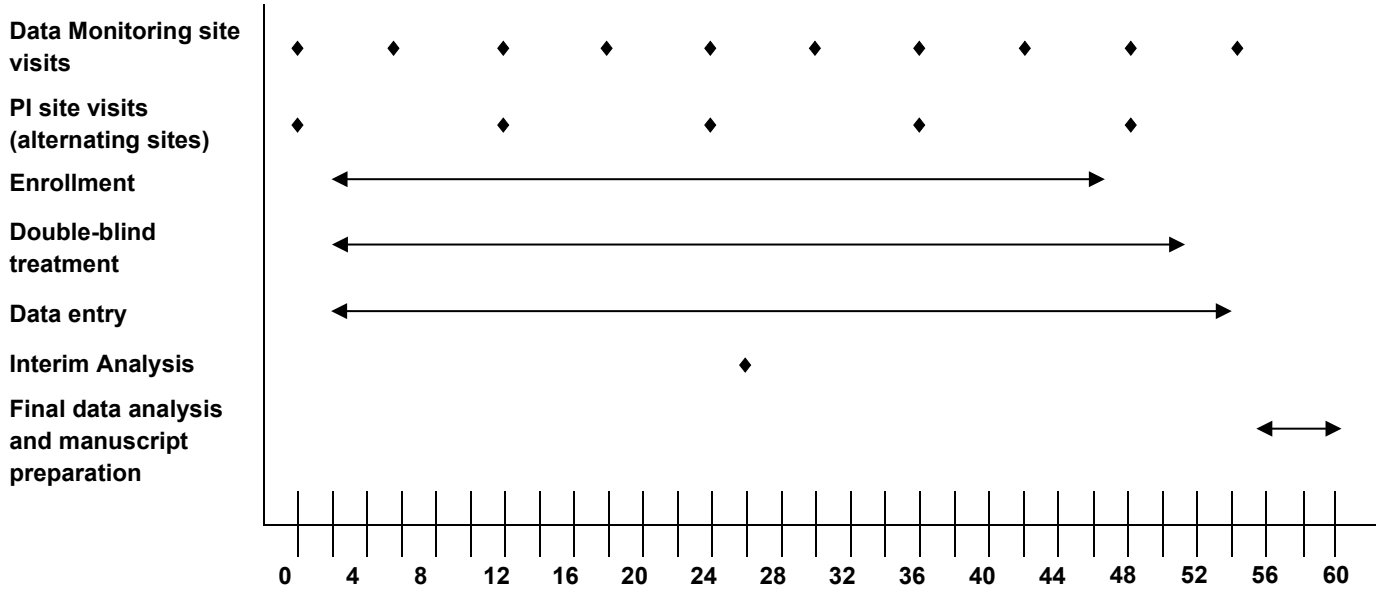
Citicoline

Week 0	250mg BID
Week 1	500mg BID
Week 2	750mg BID
Weeks 3-12	1000mg BID

Side effects will be managed in a blinded fashion as outlined in Section 3.3.b.11. At weekly visits, the $HRSD_{17}$, $IDS\text{-}SR_{30}$, YMRS, CSSRS and assessment of alcohol use will again be evaluated. All participants will receive Medical Monitoring (MM) as a psychosocial platform (section 3.3.b.10.). Participants will be paid $50 at baseline and week 12, and $30 weeks 1-11. Participants will receive $5 if they provide the optional DNA blood draw during the Baseline II visit. Participants will also receive a $2 bonus payment that increases by $2 each time an appointment is attended and resets back to $0 if an appointment is missed. Bus or rail passes will be provided when needed. After study completion, participants will be provided standard psychiatric care until outside referral is arranged. If, during Baseline 1, the participant is found to not be eligible for the study, they will receive $10 for their time.

Figure 1: Timeline for study





3.3.b.2. Inclusion/Exclusion Criteria

Inclusion:

- Outpatient men and women age 18-70 years old with bipolar I or II disorder or schizoaffective disorder (bipolar type)
- English or Spanish speaking
- Current diagnosis of alcohol use disorder with at least moderate severity (DSM-5 terminology)
- Alcohol use (by TLFB) of at least an average of 28 drinks a week if male or an average of 21 drinks per week if female and 3 drinking days a week in the 28 days prior to intake
- Diagnosis of substance use disorder other than alcohol, caffeine or nicotine is allowed if 1) alcohol is the self-identified substance of choice and 2) severity of other substance use disorder is ≤ the severity of the alcohol use disorder (DSM-5)
- If diagnosis of bipolar I or II disorder: Patient on a stable dose of a mood stabilizer therapy (lithium, lamotrigine, carbamazepine, oxcarbazepine, or an atypical antipsychotic) for at least 21 days prior to randomization or valproate/divalproex at a stable dose for at least 90 days prior to randomization, or willing to be put on a stable dose of a mood stabilizer prior to the randomization
- If diagnosis of schizoaffective disorder (bipolar type): Patient on a stable dose of an atypical antipsychotic for at least 21 days prior to randomization. An atypical antipsychotic (Risperidone) will be prescribed to participants who meet criteria for schizoaffective disorder, but are not on a stable dose of an atypical antipsychotic at the time of screening.

Exclusion:

- Mood disorders other than bipolar I or II disorders or schizoaffective disorder (bipolar type) but anxiety disorders will be allowed
- Baseline $HRSD_{17}$ or YMRS scores ≥ 35 to exclude those with very severe mood symptoms at baseline
- Evidence of clinically significant alcohol withdrawal symptoms defined as a CIWA-Ar score of ≥ 10
- Current (last 28 days) treatment with naltrexone, acamprosate, disulfiram, topiramate as these may also decrease alcohol use
- Oral contraceptives and hormone replacement therapy. This exclusion is due to a possible interaction with pregnenolone.
- Women with hormone sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, uterine fibroids. These persons are excluded because pregnenolone is converted to estrogens.
- Vulnerable populations (e.g. pregnant, nursing, cognitively impaired, incarcerated)
- High risk for suicide defined as > 1 attempt in past 12 months that required medical attention, any attempt in the past 3 months or current suicidal ideation with plan and intent such that outpatient care is precluded
- Intensive outpatient treatment (defined as ≥3 visits each week) for substance abuse (AA, NA meetings, or less intensive counseling at baseline will be allowed)
- Severe/unstable condition (e.g. cirrhosis, poorly controlled hypertension) or laboratory/physical exam findings consistent with serious illness (e.g. abnormal electrolytes) or AST or ALT >3 times normal

3.3.b.3. Discontinuation Criteria

- Change in diagnosis to other than bipolar I or II disorder or schizoaffective disorder (bipolar type) and alcohol use disorder
- Development of active suicidal or homicidal ideation with plan and intent
- Worsening in mood symptoms, that in the opinion of the investigators requires discontinuation
- If depressive or severe psychotic symptoms begin to create cognitive impairment or limited decision-making capacity. Follow up care would be arranged.
- Pregnancy
- Development of severe or life-threatening medical condition
- Involuntary psychiatric hospitalization or incarceration
- Significant alcohol withdrawal (e.g. delirium tremens) based on clinical judgment. Increases in CIWA-Ar scores will initiate a careful clinical assessment of possible worsening of withdrawal symptoms

Rationale for Protocol Discontinuation Criteria: Discontinuation criteria are designed to ensure the internal validity (e.g. accurate diagnoses) and safety (e.g. acute danger to self or others) of the study.

3.3.b.4. Recruitment and Patient Flow at Referral Sources: Recruitment can be challenging in dual diagnosis studies. By limiting enrollment to the subgroup of people with alcohol dependence who also have BPD or schizoaffective disorder bipolar type, the rate of enrollment is generally not as fast as in studies of patients with alcohol dependence alone. However, in both study sites we have had great success in recruiting this patient population using referral sources we have developed in the communities as well as free and paid advertising. The research team has conducted the largest trials in BPD and substance dependence and have conducted trials that included schizoaffective disorder (bipolar type) in addition to bipolar disorder and substance dependence. These single site studies have enrolled up to 115 participants with BPD and alcohol dependence. Given the inclusion and exclusion criteria in the proposed study both the Dallas and Miami sites conservatively estimate that they can enroll 24 participants each year in the study (48 total). Given these numbers total enrollment will take about 4 years and 2 months.

3.3.b.5. Assessments and Outcome Measures: (see Table 2 for Assessment Schedule) Research coordinators will receive training on the SCID in a 2-day course provided the UT Southwestern Psychiatry Clinical Research Infrastructure (P-CRI) (see resources section for more information on the P-CRI). A half-day reevaluation session will be conducted in years 2, 3, and 4 to maintain diagnostic accuracy. Assessments selected are available and validated in both English and Spanish.

The clinician version of the SCID is a brief structured interview for major Axis I disorders in DSM.[113] The CIWA-Ar is a 10-item, clinician-rated scale with a range from 0-67 that assesses alcohol withdrawal symptoms.[114] The $HRSD_{17}$ is an observer-rated measure of depressive symptomatology.[115] The $IDS\text{-}SR_{30}$ is a 30-item self-report scale of depressive symptom severity.[116-119] YMRS is an 11-item, observer-rated measure of manic symptoms.[120] The HRSA is a 14-item observer-rated assessment of anxiety symptoms.[121] PACS is a 5-item, self-report measure that includes questions about alcohol craving.[122] The Short Index of Problems (SIP) is a 15-item self-rated measure that assesses recent and lifetime alcohol-related problems. The SAFTEE is a 56-item self-rated scale assessing a variety of somatic symptoms. TLFB is a method for assessing recent drinking, in which participants retrospectively estimate daily alcohol consumption over a period of time ranging from 7 days to 24 months.[111, 112] The Treatment Impressions Inventory (TII) is a survey about your feelings and impressions about medical treatment. The World Health Organization/University of California at Los Angeles Auditory-Verbal Learning Test (WHO-UCLA AVLT) is designed to test verbal learning and memory. The Golden Stroop Color Word Test measures ease with which a person shifts perceptual sets to conform to changing demands and suppresses habitual responses in favor of non-dominant ones.[124] Trail Making Test (TMT) Parts A and B are tests for executive functioning, attention, sequencing, visual search, and motor function, with mental sequencing additionally required for Part B.[124] Columbia Suicide Severity Rating Scale (CSSRS) is a structured interview and rating scale used to measure suicidal ideation. An exit survey to evaluate participant's perception of in-person vs. virtual visits will be administered at week 12 or the last study visit in the event of early discontinuation.

Table 2. Assessment Schedule

Instrument	BL1	BL2	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12 Final

SCID	X													
YMRS, $HRSD_{17}$, CSSRS, TLFB, CIWA-Ar, UDS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRSA IDS-SR_{30}, PACS, SAFTEE		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, metabolic panel including AST, ALT (+ GGT, CDT), UPT	X							X						X
Lipid panel	X													X
Neurosteroid and choline levels		X												X
Optional genetics blood draw		X												
Psychiatrist assessment, vital signs, weight	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam, TII	X	(X)												
WHO-UCLA AVLT, TMT A and B, Stroop, SIP		X												X
MM		X	X	X	X	X	X	X	X	X	X	X	X	X
Exit survey														X

3.3.b.6. Raters: All research coordinators have extensive experience working with dual-diagnosis patients, and a Bachelor's or Master's degree in psychology, social work or related field. Persons acquiring data, or with any participant contact, will be blind to treatment group. To assure that these instruments are administered properly, raters will receive training on the SCID and mood assessments. We will perform group inter-rater reliability assessments annually. At the PIs (Brown) group's most recent inter-rater reliability assessment the research assistants and coordinators had an intraclass correlation coefficient (ICC) of 0.98 on both the HAMD and YMRS. As part of the startup meeting in Dallas, prior to participant enrollment, interrater reliability will be assessed on the mood measures. Additional trainings will be conducted annually via videoconferencing.

3.3.b.7. Diagnosis: Accurate diagnosis is challenging in dual-diagnosis patients. We will obtain psychiatric diagnoses based on a SCID interview and a clinical interview by a psychiatrist. When available, collateral information from family members or medical records will be used, with the potential participant's consent, as additional diagnostic information. Discrepancies between the SCID information and the information obtained from clinical interview will be resolved through discussion between the investigator, research coordinator, and potential participant. The SCID will be the source of the final diagnosis but the findings will be modified based on new information from the clinical interview. We will use DSM-5 criteria to distinguish substance-induced mood disorders and psychotic symptoms from BPD and schizoaffective disorder (bipolar type). Specifically, in the interviews we look for periods with mood and psychotic symptoms during time periods without substance use. In some cases no periods without substance use can be identified beyond childhood. Thus, using DSM-5 criteria, if all of the mood or psychotic symptoms occurred within one month of substance intoxication or withdrawal, a diagnosis of BPD or schizoaffective disorder (bipolar type) cannot be made. We acknowledge that some of the potential participants probably have BPD or schizoaffective disorder with comorbid severe and persistent substance-related disorders. However, in the interest of the internal validity of the research study, these persons will be excluded.

3.3.b.8. General Medical Evaluation: At baseline, participants will receive a laboratory evaluation that includes electrolytes, liver panel, lipids and complete blood count as well as a physical examination. Women of childbearing potential receive a urine pregnancy test and birth control information. At week 6 and at exit, participants will receive a repeat of the lab evaluation and women of childbearing potential will again receive a urine pregnancy test.

3.3.b.9. Management of concomitant psychotropic medications: Treatment of patients with the concurrent diagnosis of a major mental illness in addition to alcohol dependence requires the ability to change dosages, or add and subtract concomitant medications in the interest of participant safety, retention, and generalizability. We elected to allow changes in concomitant medications for psychiatric symptoms when clinically needed. To provide consistency to the medication management, the study physicians will take over the management of these medications and use a modification of a treatment guideline we use in several prior studies (see Human Subjects section Figure 2 for detailed guidelines).

3.3.b.10. Psychosocial platform for all participants: *All participants will receive Medical Management (MM).[125] This form of counseling has been empirically tested in combination with medications in the COMBINE study, which is the largest pharmacotherapy trial for alcoholism to date.[126] MM mimics the medication management frequently used in community settings unlike more elaborate psychosocial interventions. The primary goal of MM is to enhance medication adherence, and it is designed to be used by medically trained clinicians providing pharmacotherapy for alcoholism. MM has been empirically validated as effective when administered in conjunction with medication. MM will be delivered at medication monitoring visits by a trained study clinician. Any unscheduled crisis session or additional contact will be recorded and adjusted for in the data analysis. MM Training and Quality Control: Clinicians will be trained as described in the MM Manual. Compliance with the procedurally specified format will be monitored through supervisory sessions with Dr. Salloum.*

3.3.b.11. Procedures to Maintain the Double-Blind: Psychiatrists and raters who have contact with the subjects will remain blind in the study. One person each at the Dallas and Miami sites, with no participant contact, will maintain a group assignment list in case of emergency situations where an outside physician or clinical staff needs to break the blind. If the blind needs to be broken during the study (e.g. overdose attempt), these staff members will be available to provide this information to physicians providing emergency care. Dr. Jeon-Slaughter (DSMB support statistician) and the DSMB members will remain independent of the project team and have access to unblinded information. Raters and all persons with participant contact will be blinded to any changes in the protocol (except study discontinuation) resulting from the interim analysis (e.g. dropping a treatment arm).

3.3.b.12. Data Management: A highly experienced data manager from the UT Southwestern P-CRI (see Resources Section) will set up the database, and monitor and advise the research team throughout the study. The data manager has managed data in much larger multisite research studies. At the beginning of the study, a database format will be designed by the Dallas-based data management team in collaboration with the Miami site. A manual containing that format will be transmitted to Miami. Original data will be maintained at the site of collection (Dallas or Miami). However, de-identified data that will be used in the data analysis (e.g. depressive symptoms, alcohol use) will be stored centrally using the secure electronic REDCap system. These data will be reviewed each week by the Dallas monitor and any errors or inconsistencies will be discussed. A data monitor from both the Dallas and Miami sites will review data charts and corresponding digital database content weekly and provide feedback to the PIs and research staff on data quality and recommend remediation, if necessary. To assure consistency and accuracy between sites, the data monitor from the Dallas site will travel every 6 months to review the data collected at the Miami site. Data will be checked for errors or inconsistencies, extreme values, and missing data which will be discussed and resolved.

3.3.b.13. Blood Levels of Choline and Neurosteroids: The blood draws for these analyses will be taken at baseline and at the final visit, and the final scheduled for approximately 3 hours after the last dose of study drug. **Choline:** Citicoline is rapidly hydrolyzed to the active metabolite choline following administration. As such, we propose using plasma choline as a study endpoint as in other studies.[127, 128] Choline will be quantitated at Texas Tech University Health Sciences Center School of Pharmacy. The facility has extensive experience and specializes in analysis of drugs and metabolites contained in complex biologic matrices using mass spectrometry methods. A liquid chromatography-tandem mass spectrometry method will be transferred from the literature, developed, and validated for analysis. Choline will be extracted from plasma, and chromatographic separation will be carried out using a Shimadzu Nexera UHPLC system and reverse phase (RP) C18 column. Plasma choline content will be quantified using an AB Sciex 5500 QTRAP® in multiple reaction mode (MRM). Method development and validation will be completed in accordance with FDA Guidance for Industry, Bioanalytical Method Validation and contain studies to document (a) selectivity and specificity, (b) precision and accuracy, (c) linearity and lower limits of detection (LLOD), and (d) requisite stability studies. Choline calibration curves have been previously shown to be linear over a range of 0.05 – 5.0 µg/mL with a limit of detection (LOD) of 0.025 µg/mL. **Neurosteroids:** We will obtain circulating serum levels of allopregnanolone, pregnenolone and pregNANolone as indicators of central neurosteroid levels. In animal models, serum neurosteroid levels appear to be closely related to hippocampal levels.[129] Neurosteroid levels in serum will be determined by the laboratory of Dr. Marx at Duke University using a highly sensitive and specific gas chromatography-mass spectrometry method as described previously.[88, 130] One milliliter of serum will be extracted three times in ethyl acetate before high-pressure liquid chromatography purification using tetrahydrofuran, ethanol, and hexane in the mobile phase. Samples will be injected in duplicate. In prior work mean intra-assay coefficients of variation for pregnenolone and allopregnanolone were 0.9% and 2.9%,

respectively, and the limit of detection was 1 pg for both. With participant consent, DNA will also be obtained for future analysis. Plasma samples for DNA will be coded and sent to UT Southwestern McDermott Center for Human Growth and Development. Samples will have their DNA banked in a secure freezer with coded identification that will not include any personal identifiers such as the subject's name. Samples will begin to be analyzed when 50% (100) have been collected. When candidate genes have been suitably refined, and SNP chips become commercially available, appropriate pathways and candidate genes will be assessed via SNP chips and associated with previously assessed behaviors, personality styles, and/or biologic responses. *The neurosteroid and choline levels are essential as biomarkers and predictor of clinical response, as well as to address exploratory aim 5.*

3.3.c. Statistical Analyses Plan

Randomization: A statistician will randomize participants, stratifying by baseline drinks per drinking day of ≥ 8 and < 8 (based on use patterns in our prior studies).

General Analytic Plan: This is a study utilizing a two-stage adaptive trial design with one planned interim analysis (at end of the first stage). Two stages consist of a treatment selection stage (Stage 1) and a stage of early efficacy confirmation of the selected treatment(s) (Stage 2).[131] In **Stage 1**, participants will be randomized at a 1:1:1 ratio to receive one of the three treatments: placebo, citicoline, and pregnenolone. After 99 participants have completed the duration of treatment (completer, dropout, discontinued) an interim analysis will be performed based on the number of drinks per drinking day (primary outcome measure). Based on the interim analysis, adaptations such as stopping the trial early, re-estimating the sample size, or a different randomization scheme may be applied as recommended by the independent DSMB.

Note that a precision analysis (i.e., a confidence interval approach) will be considered for treatment selection at Stage 1.[131] *To evaluate the relative risk of making wrong decision and increase confidence in not making wrong decision at Stage 1, sensitivity analyses based on predictive confidence interval of the true difference, which is calculated using the observed difference, at interim analysis will be conducted for treatment selection.* At the end of Stage 1, one of the following decisions will be made based on the following principles:

1. The trial will be stopped if neither active treatment appears to be effective *(both active treatment effect sizes are smaller than a minimum clinically important difference, defined as an effect size of 0.25).*
2. The trial will continue to Stage 2, if there is evidence (based on precision analysis i.e., a smaller interval width) that at least one treatment from the interim analysis at end of Stage 1 is more effective than placebo. If both treatments appear to be effective in Stage 1 then the trial will continue with three-arms.

Findings from the interim analysis may result in change in sample size required for achieving statistical significance at a desired power. At the end of Stage 2, data collected from both stages will be combined for a final analysis. Depending on the results of the interim analysis, blinded sample size re-estimation may be performed per recommendation from the DSMB.

Stage 2 will be a two-arm (assuming that only one promising treatment is retained) randomized study comparing the selected treatments from Stage 1 versus the placebo. At the end of the Stage 2, the selected treatment will be compared with placebo using the number of drinks per drinking day as the primary outcome measure. At each stage, the primary efficacy analysis will be performed based on the intention-to-treat (ITT) population, defined as all randomized participants who have at least one follow-up evaluation regardless of their compliance with the protocol. In case of substantial numbers of protocol violations, a per-protocol analysis may be done to determine whether they influence the conclusions. At end of Stage 2 (or end of trial), a clinical superiority test may be performed after non-inferiority has been established, without paying any statistical penalty.

Sample size re-estimation: Sample size re-estimation will be performed based on the number of drinks per drinking day as the primary outcome measure. Sample size calculations will be performed as follows:[132]

At Stage 1, we will recruit 99 subjects (i.e., 33 subjects per arm) with 1:1:1 treatment allocation ratio, which provides clinically meaningful minimum *effect size of 0.25 between each treatment arm and placebo with* a two-sided test at the 5% level of significance. After review of interim data, an additional 100 subjects at 1:1 ratio will be recruited at Stage 2. If the effect size for *both* medications is at least 0.50 at interim analysis then we will have 81.4% power with 66 participants per arm and the study will continue with three treatment arms. To summarize: 1) If neither treatment has an effect size of at least *0.25* at interim analysis then the trial is discontinued. *This effect size was selected because it is a clinically meaningful value. Naltrexone has an average effect size of approximately 0.15-0.20 in clinical trials for alcohol dependence.[133] Thus, a useful new treatment for alcohol dependence should at least have a larger effect size than the standard treatment. This effect size of 0.25 is also an effect size at interim analysis that provides a reasonable likelihood of a significant difference from placebo at study completion assuming some increase in effect size as more participants are*

enrolled and the variance of the data decreases. 2) If one treatment has an effect size of at least *0.25* then the trial continues dropping the less effective treatment (two-arm study of one medication vs. placebo*).* 3) If both treatments have an effect size of at least 0.50 then neither treatment is dropped and the trial continues as a three-arm trial (both medications vs. placebo). This assumes that the DSMB assessment determines that the selected treatment(s) has an adequate safety and tolerability profile to continue the trial. We anticipate that the interim analysis will take place at approximately month 26 of the study. *As an incentive to enroll quickly and avoid prolonging the study, we will mandate that an interim analysis take place by month 34 even if fewer than 99 participants have been enrolled. All interim analysis decisions will be made in consultation with the NIAAA program official and DSMB.*

Statistical Methods:

The primary analysis is to assess between-group differences in alcohol use measures including drinks per drinking day (primary outcome measure), heavy drinking days, and drinking days using Generalized Estimation Equations (GEEs) analysis *with a site effect as a cluster. GEE model has been used in a prescription drug abuse treatment study with multiple site adaptive design (Weiss et al., 2010).*[106] Point estimates of the difference in the average of the number of drinks per drinking day between treatment groups and their corresponding 95% confidence intervals will be obtained. A similar analysis will be used to assess exploratory aims 1 (mood), 2 (side effects), and 3 (craving). Length of time in the study in weeks will be compared between groups using Cox proportional hazards regression (SAS Proc PHREG). Assessments only obtained at baseline and weeks 6 and 12 (e.g. GGT, AST, ALT and CDT levels) or baseline and week12 (e.g. cognitive assessments, neurosteroid and choline levels) will be analyzed using analysis of variance (ANOVA). The correlation between the reduction in alcohol use/alcohol craving and reduction in manic and depressive symptoms, *and also improvement in cognitive outcomes,* will be assessed using Pearson's or Spearman's correlation coefficient. *To address exploratory aim 6) "Determine whether changes in alcohol craving, mood or cognition occur before or after changes in alcohol use." a panel model with lagged effects*[134] *will be used to analyze 12-week longitudinal data (SAS Proc Panel) in order to explore serial correlations between changes in alcohol use and depressive symptoms or cognitive outcomes with lagged effect (e.g. one week, two week). The panel model will be constructed for each alcohol use, alcohol craving, depressive and manic symptom, and cognitive outcome and test if change in alcohol use follows changes in craving, mood or cognition at subsequent visits and vice versa.*

At each stage, a table will show the adverse events (categorized by seriousness, severity, and possible association with study drug) ordered by decreasing frequency for all patients. If appropriate, the incidence rate of adverse events will be compared by Fisher's Exact Test. Special attention will be given to those participants who have discontinued due to adverse events or experienced a serious adverse event. Exploratory analyses such as determining if baseline blood neurosteroid or choline levels predict response and whether changes in these levels are associated with clinical response will be conducted using a mixed model (SAS Proc GLIMMIX) with baseline blood neurosteroid and choline levels as fixed effects. In addition, subgroup analyses with respect to patient demographics and characteristics may be performed as deemed appropriate by the PI and/or biostatistician. Unless otherwise noted, tests of hypotheses are 2-sided and the nominal level of significance will be 0.05.

3.3.d. Dropouts: Retention is challenging in studies involving BPD/schizoaffective disorder and substance dependence. We have greatly improved our retention over the years by implementing 1) more frequent visits, 2) more frequent contact to remind participants of appointments, and 3) the use of a psychosocial platform. To minimize attrition, we will obtain multiple contact numbers, pay participants small sums at each visit, and to the extent possible have the same research coordinator and psychiatrist assess participants at each visit. In addition, data will be analyzed using an analysis that uses all of the available data and allows for missing data. We will also use a contingency management strategy in which participants are given small vouchers that increase in value with consecutive appointments attended and reset following a missed appointment. We included a similar strategy in a recently completed study in BPD and cocaine dependence (Dallas site) and observed substantial improvement in retention. We anticipate that, using the above approach and considering completion rates in both PI's studies, the proposed study will have a completion rate > 70%. Although we will make every effort to minimize missing visits and dropouts, dropouts and missing visits are common in longitudinal studies. Therefore, we will do comprehensive sensitivity analyses to investigate the consequences of incomplete observations in the analysis of repeated measurement data using local influence, pattern mixture models and multiple imputations.[135-137]

3.4. Conceptual and Design Issues

Why was drinks per drinking day selected as the primary outcome measure? Analysis of findings from prior studies in this population by the PIs suggests this is the outcome measure most sensitive to medication effects in this group of dual diagnosis patients. Data in the literature suggest that dual diagnosis patients with alcohol use disorders may have somewhat different use patterns (e.g. lower overall use but greater disability from the use) than those with alcohol use disorders alone.[138] Thus, we use an outcome measure appropriate for the patient population investigated. Please note that other alcohol use measures will also be obtained.

Why use an adaptive design rather than a convention three-arm study? 1) It is consistent with the PA. 2) It allows for fewer participants, time, and resources by reallocating resources to the more promising treatment at interim analysis. A potential disadvantage is the risk of "throwing out the baby with the bathwater" by removing one treatment at interim analysis. We minimize this risk by 1) waiting until 99 participants have been enrolled before conducting the interim analysis, and 2) allowing for both treatments to remain should they both appear to be particularly promising at interim analysis. It is important to note that should a treatment appear relatively promising on some of the alcohol, mood or cognitive outcomes, but nonetheless be dropped due to the predetermined pruning rules, information obtained is still valuable as pilot data for additional research.

How might these medications be used in a regimen for BPD or schizoaffective disorder, bipolar type and AUD? *With the exception of valproate[53], none of the mood stabilizers used for BPD or schizoaffective disorder, bipolar type have demonstrated efficacy for AUD. However, these medications have substantial side effect burdens (e.g. sedation, metabolic syndrome) and drug-drug interactions. Both of the medications proposed in this application appear to have very favorable side effect profiles and no known drug-drug interactions. In addition, both medications show promise for not only reducing alcohol use but possibly also improving mood and cognition. Thus, we suggest these would potentially be very safe and effective medications to add to existing medication regimens in a dual diagnosis population.*

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