Cover Page

Title: Exploration of Gemfibrozil as a Treatment for AUD

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1) Protocol Title (Version 1.1)

Exploration of gemfibrozil as a treatment for AUD

2) Principal Investigator

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3) IRB Review History

N/A

4) Objectives

In this pilot study, we propose to randomize 20 participants with Alcohol Use Disorder (AUD) to treatment with either placebo or 600 mg of gemfibrozil twice daily for 4 weeks in a **double-blind placebo-controlled, clinical trial.** Participants will receive 4 sessions of motivational enhancement therapy (MET)[37], regardless of medication assignment. Brain responses during response inhibition, stress, and alcohol cue reactivity will be measured with fMRI obtained at baseline and 2 weeks. Triglyceride levels will be obtained at baseline, 2 and 4 weeks. The protocol will be registered on clinicaltrials.gov.

Aim 1: To investigate the effects of gemfibrozil on alcohol use at 4 weeks in individuals with AUD. We hypothesize that relative to placebo, gemfibrozil will improve alcohol use outcomes as defined by rate of change in drinks per drinking day (DPDD), drinks per week (DPW) and percent days abstinent (PDA). Effect sizes for all 3 metrics will be calculated to determine if a larger clinical trial is warranted.

Aim 2: To investigate the effects of gemfibrozil on various possible biological targets which are increasingly recognized as important mechanisms by which treatments for AUD work. In particular we hypothesize that gemfibrozil will result in 1) increased engagement of cognitive control networks (inferior frontal gyrus (IFG) and dorsal anterior cingulate cortex (ACC)) during response inhibition, 2) decreased response in networks involved in reward (ventral and dorsal striatum, ACC) during the presentation of alcohol cues, 3) decreased response in networks that process negative affect [amygdala, insula, and ventromedial prefrontal cortex (PFC)] in response to emotional pictures, and 4) reduced triglyceride levels. We also hypothesize that changes in these targets will mediate the effects of gemfibrozil on alcohol use at 4 weeks.

5) Background

Alcohol dependence accounts for 4% of the global disease burden[1], and has significant individual and societal costs[1]. While three FDA approved medications are available for the treatment of AUD, effect sizes tend to be modest, and findings do not replicate from study to study[2-6]. Identifying additional treatments for AUD is sorely needed in order to improve the number of options available to prescribe to patients with an AUD.

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that heterodimerize with the retinoid X receptor, which, in combination, are able to modify the transcription of target genes within the cell nucleus [39]. There are three main classes of PPARs including α, β/δ, and γ, which are distributed throughout the body including the brain. In fact, PPAR α and δ are both expressed highly in regions within reward networks including nucleus accumbens, ventral tegmental area, and amygdala and also in prefrontal cortex, which may suggest a potential effect on executive control. PPAR α agonists show potential for beneficial effects on depression[9,10], neuro-degeneration[11,12], learning and memory deficits following ischemia[13], pain[14] epilepsy[15,16]

obesity[17] and inhibition/cognitive control[18]. Fibrate medications (fenofibrate, gemfibrozil), which are derivatives of fibric acid, are a class of medications commonly used in the treatment of hypercholesterolemia (especially hyperlipidemia Type III, due to its effect of lowering very low density lipoprotein) and are widely used to reduce peripheral levels of triglycerides[40,41]. Fibrates are also agonists at the PPAR α receptor.

Not surprisingly, these medications are now being explored for the treatment of addictive disorders, and particularly AUD. There have been some promising results from preclinical trials suggesting that PPAR α agonists may reduce drinking[19-22]. Blednov et al found that fenofibrate administration reduced ethanol consumption in both continuous and intermittent 2-bottle choice tests in male mice, although no effect was found for females[20]. In addition, fenofibrate and tesaglitazar administration reduced novelty responses and increased acute withdrawal, and fenofibrate increased conditioned taste aversion, all of which could explain reductions in drinking[21]. In a separate set of studies, administration of pioglitazone, a PPAR γ agonist, reduced drinking and alcohol seeking in rats[42]. Also, inadvertent reductions in alcohol consumption have been observed in trials of gemfibrozil for triglyceride reduction in humans[43]. A phase 2 clinical trial of fenofibrate administered over 9 days in non-treatment seeking individuals with at least a moderate AUD was recently completed, looking at effects of fenofibrate on cue induced craving and drinking (clinicaltrials.gov/ct2/show/ NCT02158273). However, based on results posted on clinicaltrials.gov, findings were not robust. However, no clinical trials to date have focused on testing the effect of gemfibrozil on drinking related outcomes in human subjects with AUDs.

Gemfibrozil may have some advantages over fenofibrate, and thus warrants further study. For one, although fenofibrate is more widely used due to its greater efficacy in reducing triglycerides[44], smaller effects on the CYP450 system, and lower risk for rhabomyelisis, gemfibrozil may have less liver toxicity, and both medications are equally safe[29]. Moreover, although fenofibrate showed some promise in animal models for nicotine use reduction[26,27], it did not reduce smoking in humans and only modestly reduced smoking withdrawal[28]. Importantly, fenofibrate may have limited ability to cross the blood brain barrier[23], whereas preclinical studies have shown that gemfibrozil definitively increases binding to PPAR receptors in the brain[24,25]. Gemfibrozil reaches peak plasma concentrations in humans in one to two hours post-administration and in rats, effects on gene expression are detectable in cortex within three days of use[39] suggesting a relatively fast-acting agent.

Potential targets of gemfibrozil. While the precise mechanisms of action in the brain have not been identified with PPAR α agonists, some preliminary evidence points to mechanisms that may be particularly important for AUDs, which may affect circuits involved in cue reactivity, cognitive control, and/or negative affect. *Behavioral and cognitive control:* PPAR α agonist treatment in mice improves cognitive flexibility and inhibition in a pharmacological model of ketamine-induced behavioral disinhibition and repetitive behavior in mice genetically predisposed to have repetitive behavior[18]. *Stress reactivity:* PPARα agonists have also been found to be associated with reduction in depressive behaviors in mice induced by lipopolysaccharide and in normal C57BL/6J mice[9,10]. *Alcohol Cue Reactivity:* Leptin transport across the blood brain barrier appears to be targeted by gemfibrozil[45]. Prior studies have demonstrated elevated levels of leptin in individuals with an AUD, and that these levels drop significantly after 1-2 weeks of abstinence from alcohol. Given the role of leptin in signaling satiety, increasing leptin transport could reduce craving and urges to drink. In addition to the effects on leptin transport, administration of gemfibrozil and other PPAR α agonists may affect function of neural networks involved in motivation and reward that are highly relevant to AUDs. Administration of PPAR α agonists influences gene expression in the amygdala, with a focus on GABAergic interneurons[46]. Activation of PPAR α receptors is associated with reduced firing of dopamine cells in the VTA as a result of altered activity of nicotinic acetylcholine receptors[47,48].

Triglycerides: The mechanisms by which fibrates reduce triglycerides is not fully understood; however, possible candidate mechanisms include via its effect on PPAR α in the liver, which regulates gene expression of enzymes involved in fatty acid oxidation[49], through changes in hepatic apolipoprotein CIII expression[50], through inhibition of triglyceride synthesis in the liver[51], by enhancing clearance of triglycerides[41,52,53], and potentially even through effects on dietary choice[43].

6) Inclusion and Exclusion Criteria

Individuals with AUD who are seeking treatment to reduce their drinking (N=40) will be recruited from the community through advertisements placed in local newspapers, radio stations, movie theatres, online forums, and flyers, word of mouth, and email communications directed towards community support groups.

Inclusion Criteria

1) males and females age 18-60 meeting DSM-V criteria for moderate or severe AUD in the past year
2) interested in cutting down or quitting drinking
3) able to provide voluntary informed consent
4) have at least 4 heavy drinking days (≥ 5 drinks per day for men, and 4 for women) in the past 30 days

Exclusion Criteria

1) severe liver disease; severe kidney disease; gallbladder disease or gallstones
2) chronic renal or hepatic failure
3) recent pancreatitis
4) insulin-dependent diabetes
5) other urgent medical problems
6) moderately elevated liver function tests (AST or ALT greater than 2 times upper limit of normal) or elevated creatine kinase (CK)
7) schizophrenia, schizoaffective disorder, Bipolar I disorder, suicidal thoughts in the last month
8) current moderate or severe other substance use disorder (SUD; except nicotine or marijuana)
9) active legal problems with the potential to result in incarceration
10) pregnancy or lactation, or child bearing age and not on birth control or not willing to use other birth control methods (e.g. condoms)
11) current daily use of anti-craving medications, mood stabilizers, benzodiazepines, or anti-psychotics
12) regularly taking a medication contraindicated for use with gemfibrozil including other fibrates, statins, repaglinide, or which are believed to interact with gemfibrozil such as dasabuvir, dabrafenib, loperamide, montelukast, paclitaxel, pioglitazone, rosiglitazone, colestipol, colchicine and warfarin[41,68]
13) a history of alcohol withdrawal-induced seizures or delirium tremens (hallucinations, disorientation) requiring hospital admission during the last ten years
14) a history of moderate or severe traumatic brain injury (TBI; loss of consciousness >30 minutes[69])
15) left-handedness
16) any contraindications for MRI

7) Multi-Site Research

N/A

8) Study Timelines

Individual participant's involvement will last ~15 hours over 6 weeks, which includes 4 weeks of medication/placebo. We anticipate ongoing enrollment of participants for approximately 12 months.

9) Study Endpoints

The study will close enrollment once 20 participants have been randomized. Based on previous medication trials for AUDs, we expect ~70-80% of participants will complete at least two weeks of the medication, which will be sufficient for deriving initial effect size estimates.

10) Study Methods

Participants will be asked to complete the following procedures:

Screening visit

After the participant has reviewed and signed the consent form, breath alcohol will be measured (<.01 required), participants will complete a 90 day timeline follow-back (TLFB)[71] to establish adequate drinking levels for inclusion, a handedness questionnaire[72], and a MRI safety screener to assess eligibility. In addition, participants will be interviewed using portions of the Structured Clinical Interview (SCID) for Psychotic, Anxiety, Mood, and Drug and Alcohol Use Disorders[70] to establish whether they have moderate to severe AUD and/or exclusionary SUD and psychiatric disorders. In addition, all participants will complete a urine drug screen and female participants will complete a urine pregnancy test. In addition, trained research staff will conduct a blood draw to obtain baseline levels of CBC, LFT's, BMP, triglycerides, GGT, and CK. Expected time: 2 hours

Medical history visit

If participants are eligible based on the screening visit, a subsequent visit will be scheduled for the study physician to conduct a physical examination and medical history. If not already completed at the screening visit (visit 1), trained research staff will conduct a blood draw to obtain baseline levels of CBC, LFT's, BMP, triglycerides, GGT, and CK. Expected time: 2 hours

Baseline visit

Participants who are deemed medically eligible for the study will be scheduled for a baseline appointment during which participants will complete assessments, a baseline MRI session, and the first motivational enhancement therapy (MET) session and will receive medication along with instructions for taking the medication. Expected time: Assessments (2.5 hours), MRI (1 hour), MET session (.5 hours), medication dispensing/instructions (.5 hours)

Baseline Assessments. We will collect measures of craving (Penn Alcohol Craving Scale (PACS), impaired control over drinking (Impaired Control Scale), alcohol dependence severity (Alcohol Dependence Scale)[96], nicotine dependence (Fagerstrom Test for Nicotine Dependence)[97], hazardous drinking (AUDIT)[98], intelligence (WTAR[99]), emotional regulation (Difficulties in Emotion Regulation Scale (DERS), State Difficulties in Emotion Regulation Scale (S-DERS), and Emotion Regulation Questionnaire (ERQ))[103,104], treatment alliance[105] (obtained at the end of each therapy session), motivation (Stages of Change Readiness and Treatment Eagerness Scale(SOCRATES)[106]) and outside treatment-seeking (Treatment Services Review[107]). In addition, we will collect a demographics form and a locator form to facilitate tracking of

participants. Withdrawal will be measured using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA); if participants are experiencing clinically significant active alcohol withdrawal (CIWA>8[73]), they will be asked to have their withdrawal treated before returning to initiate treatment. The Digit Span test will be used to measure working memory. To measure tendency to discount future rewards, we will use the Monetary Choice Questionnaire (MCQ) which presents participants with choices between immediate rewards and larger, delayed rewards (e.g. $10 today vs. $27 in two weeks). Depression, anxiety, and anger will be measured using the PROMIS measures of these constructs. The Drinker Inventory of Consequences (DrInC) will be administered to assess negative consequences from drinking; the results from this questionnaire will be used in the MET sessions. Finally, participants will complete a urine drug screen (all participants) and pregnancy test (females only).

An emotional working memory task will be used to assess working memory in the presence of emotional distractors (Marx et al, 2014). In the task, participants are instructed to remember letters that are superimposed onto negative, neutral, or positive pictures and judge whether the current letter matches the letter 1-back or 2-back. The total amount of time required for the task is ~12 minutes.

Functional MRI (fMRI). Participants will complete measures of neurocognitive function while undergoing fMRI that require a response after the onset of a visual or auditory stimulus. These stimuli may include pictures of alcohol or other beverages, emotional pictures (positive, neutral, negative), and different shapes (e.g. arrows, circles, squares). In addition, we will collect a rest scan, which requires participants to focus on a fixation cross.

Arterial Spin Labeling Perfusion Sequence (ASL). Quantification of cerebral blood flow (CBF) will be measured using arterial spin labeling (ASL). Because the BOLD signal may be influenced by CBF in general, we routinely collect ASL (which only adds about 5-7 minutes to the scan time) in order to assess and potentially control for general differences in CBF.

Structural MRI (sMRI). We will acquire a high-resolution protocol sufficient to permit accurate tissue classification and anatomical parcellation.

Intervention

Participants who meet study criteria will be randomized to active treatment or placebo. The placebo group will receive capsules (filled with microcrystalline cellulose powder) which look identical to capsules filled with active treatment, and will receive the same number of capsules as for active treatment. Members of the study team will be blinded to study randomization; the study pharmacist and/or another honest broker at MRN (e.g. member of the Research Operations team) will be un-blinded, and the pharmacist will not interact with any of the participants. Gemfibrozil will be prescribed at 600 mg by mouth twice daily, *which is the standard FDA approved dose used for the treatment of hypertriglyceridemia.* Adherence will be monitored with bi-weekly pill counts. At the first med dispensing visit (30 minutes, baseline), participants will receive basic information about possible side effects and will be provided with a 2-week supply. During the follow-up med dispensing visit at Visit 5 (15 minutes), individuals will undergo a review of side effects.

All individuals will also receive 4 sessions of motivational enhancement therapy (MET)[37], thus reducing ethical concerns of non-treatment. Therapists will be trained by a MINT-trained trainer.

Visit 4

One week after starting medication, participants will complete the second MET session. In addition, participants will complete TLFB, PACS, Helping Alliance Questionnaire, and the CIWA. Expected time: 30 minutes

Visit 5

Two weeks after starting medication, an additional two weeks of medication will be dispensed, the third MET session will take place, and a follow-up MRI scan (identical to baseline scanning session), blood draw, and assessments will take place. The blood draw will be used to measure LFT's, GGT, and triglyceride levels. Assessments will include the CIWA to measure withdrawal, the ICS to measure impaired control, the PACS to measure craving, the TLFB to measure drinking, the Helping Alliance Questionnaire, and medication side effects. Expected time: MET (30 minutes), MRI (1 hour), Med dispense (30 minutes), Assessments/blood draw (1.5 hours)

Visit 6

Four weeks after starting medication, the fourth MET session will take place as well as a blood draw and assessments. The blood draw will be used to measure assess LFT's, GGT, and triglyceride levels. Assessments will include the CIWA to measure withdrawal, the ICS to measure impaired control, the PACS to measure craving, the TLFB to measure drinking, the Helping Alliance Questionnaire, and medication side effects. Expected time: MET (30 minutes), Assessments/blood draw (2 hours)

Phone Call

Six weeks after starting medication, a phone assessment will be used to collect TLFB and PACS data and side effects/other symptoms that may be associated with terminating use of the medication. Expected time: 30 minutes

For all questionnaires listed above, participants may refuse to answer any question at any time. Direct identifiers will be collected and maintained in the MRN COINS database. All data collected as part of this study will be coded with a Unique Research Subject Identifier (URSI).

Instrument/Activity	Screen (Visit 1)	Screen (Visit 2)	Baseline (Visit 3)	Visit 4	Visit 5	Visit 6	Phone Call
Breathalyze	X		X		X		
SCID	X						
TLFB	X		X	X	X	X	X
MRI Screener	X		X		X		
Edinburgh Handedness	X						
Urine Drug Screen	X		X		X		
Pregnancy Test	X		X		X		
Exclusion Criteria List		X					
Medical History		X					
Physical Exam		X					
Blood draw		X			X	X	
PACS			X	X	X	X	X
ICS			X		X		
CIWA			X	X	X	X	
ADS			X				

FTND			X				
AUDIT			X				
WTAR			X				
DERS			X				
S-DERS			X				
ERQ			X				
PROMIS Anger			X				
PROMIS Depression			X				
PROMIS Anxiety			X				
MCQ			X				
Emotional WM			X				
Digit Span			X				
DRINC			X				
Helping alliance Questionnaire			X	X	X	X	
SoCRaTES			X				
Treatment Services Review			X				
Demographics			X				
Locator			X				
MRI			X		X		
Motivational Enhancement Therapy			X	X	X	X	
Medication Dispensing			X		X		
Medication Dosing Handout			X				
Medication Count				X	X	X	X
SAFETEE/Adverse events				X	X	X	X
Total time (hours)	2	2	4.5	.75	3.5	2.5	.5
Total Payment	$20	$20	$60	$10	$80	$50	$10

11) List of Appendices

ADS.doc
AUDIT.doc
CIWA-Ar_101515.docx
Demographics_031218.doc
difficultiesinemotionalregulation_scale.pdf
DrInC.pdf
Edinburgh_v09022015.doc
ERQ.pdf
Fagerstrom Test for Nicotine Dependence (FTND).doc
HelpingAllianceQuestionnaire_paper.pdf
ICS-Followup.docx

ICS-Initial.docx
MCQ_100115.docx
MRI Screening Form_no contrast_5.7.15.pdf
Penn Alcohol Craving Scale.doc
PROMISAnger.pdf
PROMISAnxiety.pdf
PROMISDepression.pdf
SOCRATESv8.pdf
StateDERS.docx
TLFB.docx
Treatment Review Questionnaire_last 30 days.doc

AdherenceHandoutPatient.docx
all_scid.pdf
Breathalyzer_UA_PregnancyResults.doc
ConcurrentMeds.doc
DigitSpan.docx
Exclusion Criteria Checklist Gemfib.docx
Locator_030918.doc
PhoneScreen_031318.docx
Physical Exam.doc
SAE_initial.pdf
SAFTEEgemfib.doc
VitalsBaseline.docx
WTAR word card.pdf

RecruitmentMaterials_flyer_v1.docx
RecruitmentMaterials_flyer_v2.docx
RecruitmentMaterials_text_advertisement_v031118.docx

gemfibrozilINDexempt.pdf
gemfibrozil_patient_brochure.pdf

12) Data and Specimen Banking

No specimens will be banked as part of this protocol. Participants will be given the option of having their data stored in the MRN Data Repository (see HRRC# 06-387, PI: Roberts).

13) Data Management

Consent Forms: Signed consent forms are stored in a locked cabinet in a locked office at MRN.

Questionnaire Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data is stored on a drive only accessible by the research team on a secure MRN server. For non-computer based forms, such as the neuropsychological assessments, the data collection sheets are stored in a locked cabinet in a locked office at MRN.

Behavioral and Imaging Data: All data is coded with the URSI, and collected and stored electronically. Electronic data is stored on a drive only accessible by the research team on a secure MRN server. De-identified data resulting from this study may also be presented at meetings, published in journals/books, used in classrooms for training/teaching purposes, and may be shared with other researchers including scientists at other universities and institutions.

Study Closure: At the time of study closure, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in radiological scans and reviews. For example, if a participant has been diagnosed with a neurological condition (e.g., multiple sclerosis, glioblastoma, etc.) it may be clinically beneficial for the participant's physician to have access to a research scan that was performed at an earlier time-point to determine disease course and severity.

In addition to the above protections, we have applied for a Certificate of Confidentiality from NIH to further protect subject confidentiality. Upon receipt of the CoC, we will revise the consent to include language that specifies that the investigators have obtained a CoC. Importantly, as stated in the consent, participants are informed that if they report current abuse of a child or an elder, we will report the person to the proper authorities, consistent with New Mexico state law.

Statistical Analysis: All MRI data will undergo standard preprocessing (e.g. motion correction, spatial normalization) and quality control prior to statistical modeling. Drinking data and other measures will be analyzed using standard statistical analyses including linear mixed models and the general linear model.

Because the proposed study is a pilot study, we will not likely have sufficient power to detect significant effects. However, we will be able to compute effect sizes for larger trials if the effects look promising.

14) Provisions to Monitor the Data to Ensure the Safety of Subjects

General Considerations: The risks are greater than minimal risk (see section 17 for anticipated risks).

Every effort will be made to identify and address adverse events as they arise from the medication treatment. At each in person follow up visit, study staff will complete the side effects checklist with participants, monitoring for any changes in anticipated side effects; these side effects will be relayed to the study physician within 1 business day. The study physician will be allowed to decrease the dose, or discontinue the study medication as deemed necessary. Similarly, every effort will be made to address adverse events as they arise from the assessments including anxiety from exposure to affective or alcohol stimuli. If there are any serious adverse events we will take appropriate measures.

If a participant does experience excessive craving or anxiety as a result of the assessments, or neuropsychological testing, or expresses suicidal thoughts, Dr. Wilcox or covering medical provider will be available at any time to assess safety and make an attempt to help the patient. Although no aspects of the study are expected to be unduly upsetting or risky, established procedures are in place for the occurrence of such an emergency. Support will be available to deal with any anxiety, fatigue or increased urge to use alcohol associated with behavioral testing. There will a physician available any time by phone to talk with participants for any emergent medical adverse events from the medication. A standardized suicide risk assessment protocol is in-use by this team to assess for safety when participants report past or current suicidal thoughts, and Dr. Wilcox or covering medical provider will be called, and one of them will be available at any time to respond, if the protocol warrants their involvement.

Every effort will be made to protect the confidentiality of participants' records. However, complete confidentiality of records cannot be guaranteed as records may be examined by authorized personnel from the approving IRB, the FDA and MRN. Otherwise, records will be

kept strictly confidential and will not be inspected by any other agency unless required by law. Loss of confidentiality will be minimized by assigning a randomized number to each participant upon entry into the study. This number will be used for all correspondence between study investigators and all data collection and analysis after the initial screening visit. MRN has state-of-the art IT networks with all necessary security mechanisms in place for data storage. Any personal information entered into computers is password protected and monitored for suspicious activity. Moreover, all information will be in double-locked rooms per privacy specifications. The results of this research may be presented at meetings or in publications; however, participants' identity will not be disclosed.

Participants will be clearly informed of their right to withdraw from the study at any time and still receive full compensation for the time they participated.

There are no known health risks associated with the proposed MRI aspect of the study. A two-way intercom system and a video monitoring system provide continual monitoring of the participant's condition at all times. If discomfort or concern is expressed, or detected, the experiment will be stopped and the participant will be given the option to discontinue at any time. Absolute caution will be implemented to ensure that only non-ferrous objects are present during all of the MRI sessions. Participants will be asked to change into hospital scrubs prior to being placed in the scanner to ensure that they do not introduce any metallic objects into the imaging environment. Participants will also be screened for the presence of a pacemaker or any other metallic objects in their body, such as an aneurysm clip, ear implant, or nerve stimulator. Participants with these or other metallic devices will not be allowed to participate in any of the previously described studies. The MRI also makes loud 'drum' beating noises during the study. Headphones or earplugs are provided for protection.

Data and Safety Monitoring Committee: Data and Safety Monitoring Committee will be established comprising the PI, study physician, research coordinator, and an external physician reviewer who is not otherwise affiliated with the study and does not report directly or indirectly to the PI. This committee will meet quarterly to review data quality, recruitment and retention, and to review all serious or clinically significant adverse events. In addition, the committee will review safety data, and follow-up on any serious adverse event that appears to be study related. The DSMC members will be blinded for participants who are currently enrolled. For all SAE's, investigators will consider and discuss the need for unblinding, based on the nature of the SAE, and based on whether or not knowing the group assignment would alter treatment of the SAE, within 48 hours. Patterns of adverse events as well as individual events may indicate the need for operational changes, protocol modifications, a decrease in dose, or, conceivably, discontinuation of the trial.

All side effects and adverse event information will be monitored for using a standardized checklist at all medication visits with the nurse or research coordinator. Study data will be reviewed quarterly, or more frequently as deemed necessary by the PI and study physician.

Adverse events (AEs) will be collected on an AE case report form when they come to the awareness of study staff. The form will include an assessment of clinical significance and study relatedness. AEs will be reported in accordance with federal law and policies and the IRB. Reporting procedures vary depending on the severity of the AE, and will follow the policies in the IRB manual. In particular, adverse events and other reportable events that are unanticipated and deemed related to research procedures and that result in greater risk of harm will be reported to the IRB within 7 days of discovery, regardless of whether they qualify as SAEs.

Serious Adverse Events: Adverse events (AEs), when present, will be collected on an AE case report form at the end of each drug administration session and at all subsequent visits. The form will include an assessment of clinical significance and study relatedness. Serious Adverse Events (SAEs) will be documented on a separate SAE form. SAEs will be reviewed by the Data and Safety Monitoring Committee at its quarterly meetings. These will also be reported to IRB within 48 hours.

15) Participant Complaints

If a participant wishes to issue a compliant or request information about the research, they may notify any study team member or the PI, Eric Claus, at (505) 272-5028, Monday – Friday from 8am – 5pm. Participants may also contact the UNM Office of the IRB, (505) 277-2644, irbmaincampus@unm.edu. Website: http://irb.unm.edu/

Depending on the nature of the complaint, the problem will be resolved directly with the participant, if possible, in a confidential and timely manner. Complaints that constitute a reportable event will be submitted to the IRB within 7 days. Participant complaints will be coded with a unique research subject identifier (URSI) and kept in their respective study folder in a locked office for record-keeping purposes.

16) Withdrawal of Subjects

Participants may withdraw from the study at any time. All unused study medication can be returned to study staff who will return it to the pharmacist for proper disposal.

17) Risks to Subjects

Gemfibrozil: The risks of the medication are greater than minimal risk. There are three main safety concerns of gemfibrozil in adults: self limited transaminitis[4], gallstones and rhabdomyelisis[2]. Our methods will allow us to explore for any adverse events in these and unexpected areas, and we will be aggressive about checking liver tests and following up concerning symptoms. We are also checking CK levels (for subclinical rhabdomyelisis) at baseline. To our knowledge there have been no clinical reports of the combinations of gemfibrozil and alcohol causing significant problems, and gemfibrozil is not contraindicated in individuals who also drink alcohol[2], although patients are warned about the risks of alcohol counteracting the triglyceride lowering effects in the package insert[2]. Moderate amounts of alcohol co-administered with gemfibrozil in rats did not cause alterations in LFTs and authors concluded that a moderate amount of alcohol with gemfibrozil is safe in rats[5]. Based on their association with gemfibrozil treatment in past work, stomach upset or pain, diarrhea, nausea, or vomiting will be monitored for using a standard checklist as well as symptoms of more serious side effects (right upper quadrant abdominal pain, nausea, vomiting would be concerning for gallstones; muscle aches or weakness, dark colored urine would be concerning for rhabdomyolisis)[6]. The FDA has determined this medication to be exempt from needing an IND (see attached IND exemption letter – gemfibrozilINDexempt.pdf).

MRI: Radio and magnetic waves associated with MRI scans are not associated with any known adverse effects. MRI is non-invasive and considered minimal risk by the FDA and OHRP. However, the scanner is a large magnet, so it could move objects containing ferrous metal in the room during the scan. All participants are screened using the MRI safety screening form prior to be being scanned. Participants may be bothered by feelings of claustrophobia (uncommon). The MRI also makes loud 'drum' beating noises during the study. Headphones or earplugs are

provided for protection. Rarely, large or recent tattoos can heat up during an MRI scan and cause skin irritation like a sunburn (uncommon). No long-term harmful effects from MRI are known. However, since the effect of MRI on early development of the fetus is unknown, participants who are pregnant will not be allowed to go in the MRI. Females will be asked to take a urine pregnancy test before being allowed to participate in the study. The test results will only be shared with participant. All MRI sequences used are within FDA approved parameters, including specific absorption rate. Due to the very high sensitivity of MRI in detecting abnormalities, there is a risk of false-positive findings, identifying something on imaging studies that may or may not be important. This may result in anxiety and a referral for additional medical testing, possibly including a recommendation for clinical scans at the participant's cost.

Blood drawing risks: Drawing blood may cause temporary pain and discomfort from the needle stick, occasional bruising, sweating, feeling faint or lightheaded and in rare cases infection or nerve pain.

General (uncommon) risks: Participation in this study may result in discomfort, emotional stress, behavioral fatigue, and inconvenience.

Privacy and Confidentiality: Participation in this study may produce emotional stress, inconvenience or an invasion of privacy (uncommon). There is also a risk of breach of data confidentiality (uncommon).

There may also be side effects or risks to study participation that are unforeseen and not known at this time.

18) Potential Benefits to Subjects

Participants may or may not have benefit from the study. Knowledge gained through this study may aid the development of more effective treatments for individuals with alcohol dependence and other addictive disorders. There are also potential direct benefits to participants in this study. All individuals (whether assigned to the active treatment with gemfibrozil or placebo group) are receiving treatment (i.e., four sessions of motivational interviewing), and will also be offered a referral list upon completion of the study. If the medication being tested works, then individuals assigned to the intervention group may also benefit from the treatment. Also, being in a research study may provide benefit, as may taking a placebo pill; individuals who undergo a series of assessments in a research study oftentimes reduce their drinking even if they are not on active treatment. Other aspects of study participation that may be beneficial include receiving free medical and psychiatric evaluations, and the attention and support of participating in a clinical trial.

19) Vulnerable Populations

No vulnerable populations will be recruited for this study.

20) Community-Based Participatory Research/Field Research

N/A

21) Sharing of Results with Subjects/Incidental Findings

All research MRI scans are read for incidental findings by a radiologist unless the individual has been scanned at MRN in the previous six months. If the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying

information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions.

22) Research Setting

All study procedures and participant interactions will take place at the Mind Research Network. Study medication will be stored in a locked cabinet in a locked room once dispensed from the pharmacy. Blood samples will be processed at Tricore.

23) Resources Available

The PI and study team are all experienced neuroimaging researchers. John Phillips serves as MRN Medical Director. Located on UNM's north campus, MRN is a 501(c)3 non-profit organization consisting of an interdisciplinary association of scientists focused on state-of-the-art imaging technology and its emergence as an integral element of neuroscience investigation.

Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities also have private changing rooms with lockers for personal items. In addition, there is a space for conducting blood draws that provides privacy to participants while they complete the blood draw. All MRN research staff are trained in regards to the HIPAA Privacy Rule. All individuals will be trained to administer the same consenting and study procedures. Further, all study personnel will have current CITI and HIPAA training throughout the period of the study.

24) Prior Approvals/Attachments Requiring Signatures

MRN Departmental Review

25) Recruitment Methods

1.1 Describe when, where, and how potential subjects will be recruited.

Participants may be recruited through flyers, radio/TV ads, press releases, newspaper ads, business cards, and online postings (e.g. Craigslist, Google Adwords, Facebook, Instagram, clinicaltrials.gov) within the Albuquerque metro area. Approved study recruitment text and flyers will be used in digital recruitment mediums, such as university list-servs, online advertising mediums, or digital presentation slides. The study may also recruit using approved text/images on stickers that can be placed on paper bags and distributed at liquor stores, and study logos/information placed on bottle openers, drink koozies, and other drinking-related paraphernalia which can be handed out during local festivals (e.g. brewfests, wine festivals, state fairs, etc). Word of mouth from current and past participants, employees and collaborators, as well as other individuals will also be used and may include sharing approved information and/or recruitment materials. Finally, participants from other studies who have expressed an interest in being contacted for future studies, including from the MRN Participant Recruitment Registry, may be contacted to determine eligibility and interest in this study.

1.2 Describe the source of subjects.

Participants will be volunteers from the community.

1.3 Describe the methods that will be used to identify potential subjects.

Potential subjects will be self-selected and must contact the laboratory to express initial interest in the study. Once initial contact is made, research staff will explain the study and conduct a brief phone screen interview. Also, participants from other studies who have expressed an interest in being contacted for future studies, including from the MRN Participant Recruitment Registry, may be contacted to determine eligibility and interest in this study.

1.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Recruitment materials are included with the application (attachments are listed below).

Brief_advertisement_v031118.docx
Flyer_v1.docx
Flyer_v2.docx

26) Local Number of Subjects

We anticipate phone screening up to 100 individuals and may enroll up to 50 participants in order to obtain a final sample size of 20 participants who complete the study.

27) Confidentiality

All participants are assigned a study ID (URSI) that links their data with their name and other identifying information. All study data (with the exception of the consent form and payment receipt) are coded only with this number. The information is maintained in a secure, restricted access database. After completion of data analysis, the linking code will be made inaccessible to the research team. De-identified data will be retained until data analysis activities are complete.

28) Provisions to Protect the Privacy of Subjects

Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. The imaging facilities also have private changing rooms with lockers for personal items.

29) Compensation for Research-Related Injury

No commitment is made by the MRN to provide free medical care or money for injuries to participants in this study. This is clearly stated in the consent form.

30) Economic Burden to Subjects

Participants will not be charged for any of the experimental study procedures, including MRI scans. If incidental findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

31) Consent Process

Upon initial contact, the study will be briefly introduced to the participant by a member of the research team. Participants will then be screened over the phone or in person. Identifiable information will be retained for those participants who do not meet inclusion criteria only for the duration of the study to ensure that the same participant does not attempt to enroll a second time. If the participant meets inclusion criteria, the study visit will be scheduled and an informational brochure and copy of the consent document will be sent to them if requested. Participants requesting the consent ahead of their visit will be allowed as much time as they need to decide whether or not to participate, and the PI or study staff will be available to answer questions about the consent/study procedures while the participant is making their decision. When the participant arrives for their appointment, the participant will be seated in a private room and given time to read the consent form. After the participant has finished reading the consent form, the study is described more fully by the research team and the participant is asked whether they have any questions regarding the described procedures and risks/benefits. Participants must elect to participate and can choose to discontinue their participation in the study at any time. If requested, we will show the participants the equipment that will be used to perform the study. In addition, we may ask some basic questions of the participants about the proposed study to ensure that the participants understand the nature of the experiment. No coercion or undue influence will be used.

If there are no further questions, the consent form is signed and stored in a locked cabinet in a locked office at MRN. A copy of the consent will be given to the participant.

32) Drugs or Devices

All medications will be stored and handled by the research pharmacy and only staff trained to dispense medications including the research coordinator or study physicians will dispense medications. Medications will be dispensed at Visits 3 and 5, and pill counts/medication adherence will be measured at Visits 4-6. In addition, participants will be asked to report on adherence on the follow-up phone call.

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