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NCT04098302: Dutasteride Treatment for Reducing Heavy Drinking in AUD: Predictors of Efficacy

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Alcohol Research Center
Department of Psychiatry
University of Connecticut School of Medicine
Farmington, CT 06030-1410

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Principal Investigator: Jonathan Covault, MD, PhD
Co-investigators: Howard Tennen, Ph.D., Surita Rao, MBBS,

Abstract

Heavy drinking remains a significant public health problem and is frequently under treated. Although several medications have been shown to help patients stop or reduce drinking, additional medication options are needed as there is considerable variability in effectiveness or tolerability of existing medications for individual patients. Additionally, identification of individual subject level predictors of efficacy are needed to better personalize pharmacotherapy treatment recommendations. This study will seek to replicate and extend our results showing efficacy of a novel medication dutasteride for reducing drinking and will examine potential easily measured predictors of response.

Dutasteride is a widely prescribed medication for benign prostatic hypertrophy and androgenic hair loss that also modulates the elimination of cortisol and the production of some neuroactive steroids. Changes in the regulation of cortisol and neuroactive steroids have each been suggested as factors which may contribute to the maintenance of alcohol dependence. Data from a recently completed first randomized placebo controlled trial of dutasteride for AUD in a sample of male drinkers, indicates that dutasteride is well tolerated in alcoholics and has efficacy in helping subjects reduce drinking. Additionally, results indicate that dutasteride may be particularly helpful for patients who drink to cope with anxiety and negative emotions, a group of patients with poor response to other treatments.

This 24-week treatment study will use an innovative randomized placebo controlled step therapy design to examine the safety and efficacy of dutasteride to reduce drinking among a sample of 190 treatment seeking women and men with hazardous levels of alcohol use. At 12-weeks placebo non-responders will transition to dutasteride and dutasteride non-responders will transition to naltrexone, an FDA approved medication with demonstrated efficacy for reducing heavy drinking. 12-week responders (reduction in drinks/week of 60% or greater compared with screening) will continue for an additional 12-weeks on their initial study medication assignment (dutasteride or placebo).

Additionally, we will examine several baseline measures as predictors of dutasteride efficacy, including drinking to cope, anxiety, adverse child events, and perceived life stress as well as stress resilient vs. reactive genotypes of FKBP5 a chaperone protein involved in regulation of glucocorticoid, androgen and progesterone receptor function.

Section 1.

Alcohol has multiple biological effects, each of which are potential targets for pharmacotherapy of alcohol use disorder (AUD). Human and animal studies indicate that alcohol-induced generation of $GABA_A$ receptor neuroactive steroid agonists mediates some of alcohol's effects and that chronic alcohol use leads to disturbances in HPA axis function. Dutasteride, a widely used medication to treat benign prostatic hypertrophy, is an inhibitor of 5-alpha reductase (5AR) enzymes, which play a central role in the production of neuroactive steroids as well as in the elimination pathway for cortisol. Thus, dutasteride represents a potential pharmacologic treatment for AUD. Results from the first placebo (pbo)-controlled, randomized study of dutasteride for treating AUD conducted at UConn Health Alcohol Center show that dutasteride 1 mg/day was efficacious in reducing the number of heavy drinking days and drinks per week in treatment-seeking, non-smoking men. During the final 4 weeks of the 12-week treatment phase, 49% of subjects in the dutasteride arm had reduced their drinking by ≥60% compared with 20% of pbo-treated subjects [χ^2=8.3, p=0.004; OR=3.8 (95% CI=1.5-9.8)] and 33% of subjects in the dutasteride arm had zero heavy drinking days compared with 11% of pbo-treated subjects [χ^2=6.7, p=0.01; OR = 4.1 (95% CI=2.0-12.5)]. This treatment response represents a moderate effect size comparable to that observed in a previous study led by Dr. Kranzler and Covault of topiramate for reducing heavy drinking previously conducted at UCONN Health Alcohol Research Center (Kranzler, Covault et al. 2014). We also identified potential predictors of dutasteride treatment efficacy. Subjects with elevated baseline drinking to cope motivation and anxiety showed a greater dutasteride vs. pbo treatment response. This finding suggests that dutasteride may facilitate reduced drinking in part by modulating HPA stress response pathways as hepatic 5α-reductase and 5β-reductase and adipose 5α-reductase are important components of the cortisol elimination pathway. These findings warrant additional study of dutasteride as a new treatment option for AUD. This proposal seeks to extend these findings by:

a) examining the safety, tolerability and efficacy of dutasteride to reduce drinking in a sample including both men and women in a 12-week pbo-controlled, randomized study *phase 1*;

b) examine whether the reduction of drinking in phase 1 initial 12-week treatment responders (defined as ≥60% reduction in drinks/wk during weeks 9-12) can be maintained in a 12-week double blind *phase 2* extension of the initial treatment condition to help identify the clinical utility of dutasteride as a treatment for AUD, which is a chronic relapsing disorder;

c) examine whether pbo arm non-responders during phase 1 experience a reduction in drinking when crossed over to dutasteride during the 12-week *phase 2* extension; and

d) examine the moderating effects on treatment outcomes of baseline self-reports of drinking to cope, trait anxiety, perceived stress, adverse child experiences and a polymorphism (rs1360780) in the *FKBP5* gene encoding a key chaperone protein regulating functions of androgen, progesterone and glucocorticoid receptors that has been

associated with negative behavioral responses to life stressors, including increased heavy drinking in college students (Lieberman, Armeli et al. 2016) and a stronger linkage between drinking to cope and next day emotional depletion.

Specific Aims.

Aim 1. To examine the safety, tolerability and efficacy of dutasteride in helping patients with AUD to reduce or stop drinking, 190 treatment-seeking men and women with AUD who drink heavily on a regular basis (≥24 standard drinks / week for men and ≥18 drinks/week for women) will be randomly assigned to treatment with either dutasteride or pbo for 12 weeks. A biological marker (PEth phosphatidylethanol) will be used as a secondary measure of change in alcohol use and the dihydrotestosterone (DHT) metabolite 3α-androstanediol glucuronide will be used to monitor dutasteride inhibition of 5α-reductase enzyme activity. We hypothesize that dutasteride 1 mg/day will be well tolerated by both male and female heavy drinkers, will produce ≥80% reduction in the serum marker of 5α-reductase enzyme activity and will result in a greater reduction in the number of heavy drinking days and drinks per week than pbo and that treatment effects will be greater for women as they are expected to more frequently experience drinking to cope, higher anxiety and a history of childhood adversity/trauma.

Aim 2. Aim 2A: To examine whether the reduction in drinking in treatment responders (defined as ≥60% reduction during weeks 9-12) is maintained in a 12-week, phase 2 extension of the initial treatment condition (pbo or dutasteride). This will help to determine the clinical utility of dutasteride as a treatment for AUD, which is a chronic, relapsing disorder. Aim 2B: Increase the number of dutasteride double-blind treated subjects by including in the 12-week phase 2 a cross-over for pbo non-responders to dutasteride and for dutasteride non-responders to naltrexone, a medication with a different mechanism of action compared with dutasteride.
We hypothesize that reductions in drinking for dutasteride responders in phase 1 will be maintained during the 12-week extension period. Additionally, we hypothesize that phase 1 non-responders on pbo will have significant reductions in drinking when crossed over to dutasteride in the second 12-week phase. Further, we expect that a portion of dutasteride non-responders will have significant reductions in drinking when treated with naltrexone, consistent with models of individual genetic and environmental factors producing differences in individual subject responses to medications with different mechanisms of action.

Aim 3. To examine baseline measures of drinking to cope, trait anxiety, perceived life stress, or early life adversity predict dutasteride treatment efficacy, and secondarily, whether a common genetic variation, rs1360780, in the *FKBP5* gene, which encodes a modulator of the intra-cellular steroid hormone signaling system and HPA stress response system, moderates dutasteride treatment response as an interactive effect with these negative affect/life stress measures. We hypothesize that dutasteride treatment benefits

relative to placebo will be greatest for subjects reporting more drinking to cope, greater anxiety, perceived stress or a history of trauma/adversity, particularly for those who are carriers of the *FKBP5* rs1360780 T-allele.

Section 2. RESEARCH STRATEGY

2.A. Significance. Alcohol use disorder is highly prevalent, frequently chronic and has significant negative effects on the health and quality of life for affected individuals and their families. Alcohol use has been estimated to account for 4.6% of lost global disability-adjusted life-years (Rehm, Mathers et al. 2009). Alcohol use disorder (AUD) has a point prevalence of 14% in the U.S. (Grant, Goldstein et al. 2015) and is notably undertreated. Most problem drinkers do not seek treatment and those who do are frequently more interested in reducing rather than stopping drinking. Primary care providers often feel hesitant or ill-prepared to intervene using psychosocial treatments other than referral to AA and may be more willing to provide medical therapies. Pharmacotherapy options for alcohol use disorder include only three FDA-approved compounds (disulfiram, naltrexone and acamprosate), which have modest effect sizes compared with placebo (Zindel and Kranzler 2014). Recent studies highlight the potential for medications approved for the treatment of other indications (e.g., topiramate, ondansetron, zonisamide, baclofen) to be applied to the treatment of AUD (reviewed in references (Edwards, Kenna et al. 2011, Zindel and Kranzler 2014, Akbar, Egli et al. 2018)). Study of additional agents, particularly those that act through novel mechanisms, is needed to expand the range of pharmacotherapy options for AUD. The neuroactive steroid system represents one such novel mechanism, and dutasteride, a widely prescribed medication that blocks a key step in the production of 5α-reduced neuroactive steroids, is a promising candidate for treating AUDs. In the first RCT of dutasteride (section 2.B.2) we observed that patients reporting drinking to cope, higher levels of anxiety or taking medications for depression or anxiety may particularly benefit from dutasteride. Co-morbid symptoms of anxiety and/or depression are common among treatment seeking drinkers and are associated with worse treatment outcomes (Smith and Randall 2012). Drinking to self-medicate anxiety and mood symptoms increases the risk of AUD incidence and persistence (Menary, Kushner et al. 2011, Crum, Mojtabai et al. 2013) and drinking to cope appears to be a keystone feature linking internalizing symptoms with adverse drinking-related outcomes (Armeli, Sullivan et al. 2015, Anker, Forbes et al. 2017). Women drinkers are more commonly affected by anxiety/depression and drinking to cope (Smith and Randall 2012).

This study aims to extend our findings by examining effects in both men and women, extending treatment period to 24 weeks and to examine baseline measures, including drinking to cope, perceived stress, anxiety and childhood adversity alone or combined with a polymorphism in the gene encoding the steroid hormone receptor chaperone protein FKBP5, to predict patient groups most likely to benefit from dutasteride compared with placebo. Identification of phenotypic and genetic predictors of medication response offers the potential to personalize alcohol treatment (Jones, Comer et al. 2015, Seneviratne and Johnson 2015) as it is common experience in clinical practice that

medications have limited benefit for the average patient, but in a subset of patients can have large effects.

2.B. Innovation. The study is innovative in examining a novel medication, dutasteride, for AUD and for identifying predictors of response to advance the personalized treatment of the disorder. The study design is innovative, as it employs a 24-week pharmacotherapy protocol with a sequenced medication treatment algorithm to allow a naturalistic approach to treatment and enhance retention. Specifically, patients who respond to their initial treatment during the initial 12 weeks (phase 1), will continue on that assigned treatment with continued blinded conditions. However, patients who fail to respond during phase 1 will transition in a pre-planned fashion to either dutasteride for those who received pbo in phase 1, or naltrexone for those who received dutasteride in phase 1. Naltrexone is an FDA approved medication for AUD with a completely distinct mechanism of action compared with dutasteride and which has been reported to have greatest benefits for smokers (Fucito, Park et al. 2012, Schacht, Randall et al. 2017) and patients with greater drinking to enhance compared with drinking to cope (Mann, Roos et al. 2018) characteristics which complement those we have identified for dutasteride (see 2.B.2). This design provides a blinded and ethical solution for retaining patients in a 6-month treatment study for those who fail to respond in the initial 3-month phase and provides additional information on the utility of the investigational medication dutasteride by exploring the effects of crossing placebo non-responder to dutasteride for phase 2 of the study.

2.B.1. Neuroactive steroids, dutasteride and alcohol. An extensive body of pre-clinical research supports the hypothesis that endogenous neuroactive steroids produced in response to alcohol mediate some of the behavioral and electrophysiological effects of alcohol [reviewed in (Kumar, Porcu et al. 2009). 5α reduced 3α-hydroxy-pregnane and 3α-hydroxy-androstane neuroactive steroid metabolites of progesterone and testosterone respectively are endogenous, highly potent, positive allosteric modulators of $GABA_A$ receptors (Paul and Purdy 1992) that are produced both peripherally and in the brain. Immunostaining studies examining rodent and cynomolgus monkey brain tissue indicate that levels of 3α-reduced neurosteroids are dynamically regulated in the CNS and show regional variation (Saalmann, Kirkcaldie et al. 2007, Beattie, Maldonado-Devincci et al. 2017, Beattie, Reguyal et al. 2017). While 5α,3α-reduced steroids have been more widely examined as they are the prevalent form in rodents, in humans 5β,3α-reduced steroids are also present and are also positive allosteric modulators of $GABA_A$ receptors (levels of these would not be reduced by 5α-reductase inhibitors).

In rat models, alcohol increases levels of neuroactive steroids in the plasma and brain of intact animals and in brain slice preparations (Barbaccia, Affricano et al. 1999, Morrow, Janis et al. 1999, VanDoren, Matthews et al. 2000, O'Dell, Alomary et al. 2004, Sanna, Talani et al. 2004). Blockade of ethanol-induced increases of neuroactive steroids in rats using the 5-alpha reductase (5AR) inhibitor finasteride attenuates several

behavioral effects of alcohol (VanDoren, Matthews et al. 2000, Hirani, Khisti et al. 2002, Hirani, Sharma et al. 2005) and blocks the effects of alcohol on $GABA_A$ currents in brain slice preparations (Sanna, Talani et al. 2004). Other studies have examined the effects of neuroactive steroids and their inhibitors on alcohol self-administration in rodents. In mice and rats trained to self-administer 10% ethanol, treatment with low doses of the endogenous $GABA_A$ neurosteroid agonist allopregnanolone (5α-pregnan-3α-ol-20-one) (Ford, Nickel et al. 2005) or the synthetic neurosteroid agonist ganaxolone (Besheer, Lindsay et al. 2010) increase alcohol self-administration. In contrast, treatment with the $GABA_A$ inhibitory neuroactive steroid epipregnanolone (5β-pregnan-3β-ol-20-one) reduces alcohol self-administration in rats (O'Dell, Purdy et al. 2005). Additionally, blockade of neuroactive steroid production by the 5AR inhibitor finasteride attenuates the acquisition of alcohol preference in mice (Ford, Yoneyama et al. 2008) and reduces alcohol self-administration in mice previously trained to self-administer it (Ford, Nickel et al. 2005), as well as in naïve mice (Ramaker, Ford et al. 2011). Together, these results from pre-clinical studies suggest that 1) alcohol-related changes in neuroactive steroid levels or patterns of metabolism contribute to the reinforcing aspects of alcohol in self-administration paradigms and 2) that blockade of these processes by inhibitors of 5AR may be useful in reducing alcohol consumption in humans.

Data from human studies supporting neuroactive steroids as mediators of alcohol's effects are more limited. In humans, the plasma concentration of allopregnanolone has been reported to be increased following severe intoxication (Torres and Ortega 2003, Torres and Ortega 2004), but not moderate doses of alcohol (Holdstock, Penland et al. 2006, Pierucci-Lagha, Covault et al. 2006, Porcu, O'Buckley et al. 2009). We provided indirect evidence of a role of neuroactive steroids in human alcohol consumption by showing that polymorphisms in two key neuroactive steroid biosynthetic enzymes, 5AR type I (encoded by *SRD5A1*), and 3α-hydroxysteroid reductase type 2 (encoded by *AKR1C3*) are associated with AUD (Milivojevic, Kranzler et al. 2011). Further, we found that His5→Gln *AKR1C3*2* C-allele (an AUD risk allele) homozygotes reported lower effects of acute alcohol in a human laboratory study (Milivojevic, Feinn et al. 2014).

Finasteride, which has been widely used as a pharmacological tool in animal studies of neuroactive steroids, blocks both type I and II 5AR in rodents. However, in humans, finasteride at clinical doses blocks only type II 5AR, the 5AR isoenzyme most abundant in prostate and skin but absent in adult brain. Dutasteride, a second FDA-approved 5AR inhibitor for the treatment of prostatic hyperplasia, irreversibly inhibits both type I (brain, adrenal, liver and adipose tissue) and type II (liver, skin and prostate) 5AR enzymes at clinically relevant dosages, leading to a greater reduction in 5α-dihydrotestosterone (DHT) levels than finasteride without suppressing testosterone (Clark, Hermann et al. 2004). This broader 5AR inhibition profile, together with good tolerability and safety, make dutasteride an excellent candidate medication for reducing drinking in humans. Published reports of the behavioral effects of dutasteride in humans support the potential clinical utility of dutasteride beyond effects on DHT levels in prostatic hyperplasia and alopecia. In a study of male social drinkers, we reported that a single 4-mg dose of

dutasteride reduced the sedative effects of alcohol consumed 2-4 days later and also reduced drinking in the natural environment for 1-2 weeks following this short treatment (Covault, Pond et al. 2014). A pilot study in women with pre-menstrual dysphoria showed that dutasteride 2.5 mg daily for 30 days was well tolerated and attenuated pre-menstrual dysphoria symptoms (Martinez, Rubinow et al. 2016).

In addition to the well-known role of 5AR enzymes in conversion of testosterone to dihydrotestosterone, 5AR (and 5β-reductase) enzymes inactivate cortisol to 5-dihydrocortisol, which is then converted to the inactive elimination cortisol metabolite 5-tetrahydrocortisol (5a/b-THF) by 3-hydroxysteroid dehydrogenase. 5α-THF and 5β-THF each represent ≈20% of total urinary excretion of cortisol metabolites (Finken, Andrews et al. 1999). Dutasteride and finasteride treatment for 3 months in healthy subjects reduces levels of 5α-reduced cortisol urinary metabolites by over 95% without an increase in 5β-reduced cortisol metabolites resulting in an overall reduction of urinary cortisol metabolites but without a change in morning plasma or salivary cortisol (Upreti, Hughes et al. 2014). This recent finding suggests that 5AR inhibitors reduce overall adrenal cortisol output by reduction in rates of elimination with compensatory cortisol feedback reductions in further HPA axis activation and suggests that dutasteride would be expected to reduce the plasma ACTH to cortisol ratio. HPA effects are thus a second mechanism by which dutasteride could moderate alcohol intake which may be most relevant to patients with elevated stress, stress reactivity, anxiety or trauma (Blaine and Sinha 2017).

2.B.2. Preliminary studies.

We recently completed the first RCT of **Dutasteride for the reduction of heavy drinking in men.** Results support further examination of dutasteride as a treatment option for AUD. In total 189 treatment seeking men were enrolled of which 24 were screen failures and 23 failed to return for the baseline visit leaving 142 subjects randomized to medication (dutasteride n=74). Seven subjects did not return after the baseline randomization visit providing a modified intention to treat sample of 135 subjects (68 dutasteride and 67 placebo) who provided drinking data post-randomization. One hundred seven subjects completed the entire 12-week treatment. The mean number of treatment weeks completed were not different between arms (dut 10.2 vs. pbo 10.7). 3α-androstanediol glucuronide levels were decreased by 80% in the dutasteride group at both 6 and 12 weeks vs. 0% in pbo treated subjects confirming the anticipated pharmacological effect for our study design. There were no significant differences between groups (dutasteride vs. pbo) for measures of alcohol consumption during the 60-days prior to screening including the number of standard drinks (SD) per week (48.8 vs. 47.3), number of heavy drinking days (HDD, 5 or more drinks for men) per week (5.2 vs. 5.2), or abstinent days per week (0.67 vs. 0.62). While the dutasteride group were more likely to have had a prior episode of treatment for alcohol use (59% vs. 40%, p=0.03) the number of DSM-IV AD criteria did not significantly differ between groups (4.3 vs. 4.0).

Safety. There were no study related serious adverse effects. The proportion of subjects exposed to study medication who reported at least one non-serious adverse

effect was not significantly different for the dutasteride vs. pbo groups 71.6% vs. 67.1% similarly, the number of side effects per subject was not different between dutasteride and placebo groups, 1.36 ± 1.46 vs. 1.03 ± 1.10. Adverse events that were reported by more patients in the dutasteride compared with the placebo arm included stomach discomfort (16.4% vs. 4.5%, p=0.04) and reduced libido (9.0% vs. 0%; p=0.03). More subjects in the dutasteride arm (n=4) than the pbo arm (n=1) stopped medication due to side effects. Beck Depression Inventory scores were low in both treatment arms at baseline (10.4 dut vs. 7.5 pbo) and reduced to a similar degree during the 12-week treatment (-3.3 dut vs. -2.4 pbo, t=0.6; p=0.5).

Drinking outcomes. Comparison of treatment groups for the modified intention to treat sample (N=135) on the primary outcomes of HDD/week and drinks/ week using generalized linear mixed models (GLMM) showed significant treatment x time interactions (HDD F=9.2; df=1,1406, p=0.002 and SD/wk F=4.8, df=1,1406, p= 0.028).
While a minority of our subjects smoke, in view of prior reports of differential medication effects among smokers vs. non-smokers for naltrexone we examined GLMM models that included smoking status, treatment condition, treatment x time, and treatment x smoking as predictors, and identified significant 2-way interactions of treatment x time (F=9.1, df=1,1404, p=0.003 and F=4.4, df=1,1403, p=0.035 for HDD and SD/wk, respectively), and treatment x smoking (F=8.4, df=1,1404, p=0.004 and F=10.9, df=1,1403, p=0.001 for HDD and SD/wk, respectively), such that smokers (n=12) treated with dutasteride drank more throughout the treatment period than smokers treated with pbo (n=12), while the opposite response was observed for non-smokers (dutasteride=56; pbo=55). Smokers and non-smokers did not differ on baseline drinking, age, Spielberger State Anxiety (SAI) or Beck Depression Inventory (BDI) scores. The interaction of drug x smoking status may relate to the induction by tobacco of phase I metabolism cytochrome P450 and aldo-keto reductase enzymes (Nagaraj, Beckers et al. 2006), the latter of which are involved in neuroactive steroid biosynthesis and metabolism. A prior study showed a positive correlation between serum cotinine levels and the neuroactive steroid allopregnanolone in a sample of 28 men (Marx, Trost et al. 2006). Somewhat surprisingly, with limited exceptions (Fucito, Park et al. 2012, Litten, Ryan et al. 2013, Schacht, Randall et al. 2017) reports for recent RCTs for AUD either did not report the proportion of smokers (Johnson, Ait-Daoud et al. 2003, Johnson, Rosenthal et al. 2007, Johnson, Ait-Daoud et al. 2011, Johnson, Seneviratne et al. 2013, Kranzler, Covault et al. 2014) or did not include smoking status in the analysis of outcomes (Anton, O'Malley et al. 2006, Anton, Myrick et al. 2011, Fertig, Ryan et al. 2012, Litten, Fertig et al. 2012). Interestingly, in the reports by Fucito et al. (Fucito, Park et al. 2012) and Schacht et al.(Schacht, Randall et al. 2017) naltrexone only benefited drinkers who also smoked while our results with dutasteride indicated only non-smokers were responsive, presumably reflecting distinct mechanisms of change. We will include smokers in the proposed study to further evaluate our initial findings. Dutasteride non-responsive smokers in phase 1 may experience treatment responsive to naltrexone in phase 2 of the proposed study which would support use of smoking as a factor in individualized treatment recommendations.

For the majority non-smoker group (n=111) there was a significant interaction of medication group by treatment week (HDD/wk F=6.2, df=1,1183, p=0.013; and SD/wk F=4.7, df=1,1183, p=0.031) **Figure 1,** such that dutasteride treated subjects reduced drinking over time more than placebo subjects. During the last 4 weeks of the 12-week treatment period, the proportion of subjects with a ≥60% reduction in SD/wk compared with screening (which represents a clinically meaningful reduction from a group average of 48 SDs/wk to less than 20) was significantly greater for the dutasteride vs. the pbo group [49% vs. 20%; χ^2=8.3, p=0.004; OR=3.8 (95% CI=1.5-9.8)]. Additionally, among the 91 per protocol completers, during the last month of treatment 33% of subjects in the dutasteride arm had no heavy drinking and 27% no hazardous drinking (no HDDs and no more than 14 SD/wk) compared with 11% and 2% of pbo- treated subjects respectively [no HDD days [χ^2=6.7, p=0.01; OR = 4.1, NNT=5]; and no hazardous drinking [χ^2=11.1, p=0.001; OR = 16.4, NNT=4]. The additional analysis described below focuses on the group of 111 non-smokers.

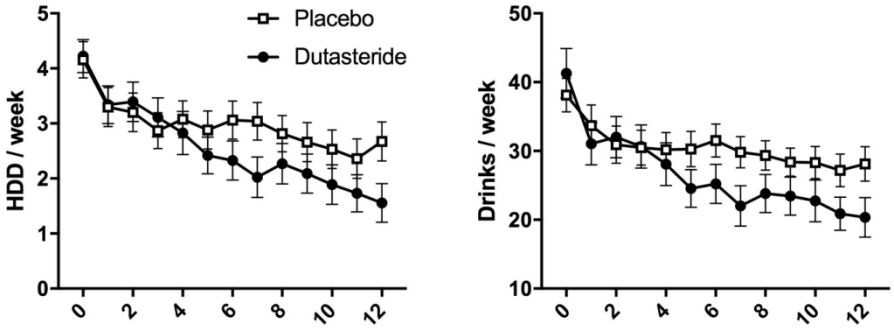

Figure 1. Heavy Drinking Days per week (left) and Standard Drinks per week (right) for pbo vs dutasteride treated non-smokers (mean±SEM).

Potential predictors of response: In an effort to identify potential drinking related markers associated with treatment response we examined several measures collected at study entry including drinking motives (CDMQ), self-reported alcohol cravings, and family history of AD (a surrogate for genetic loading). Among these features, only the CDMQ drinking to cope score significantly interacted with medication group. There was a significant interaction of medication with baseline drinking to cope score for HDD/wk (F=10.2, df=1,1155, p=0.001) and for SD/wk (F=4.9, df=1,1155, p=0.027) such that contrasting subjects above and below the median drinking to cope groups, there were limited reductions in drinking in the higher DTC group among placebo subjects but significant drinking reductions in dutasteride treated patients, **Fig. 2**. For the high drinking to cope group there was a significant medication x time interaction for the HDD/wk measure (F=5.6, df=1,535, p=0.017) and a significant main effect of medication for SD/wk (F=5.2, df=1,535, p=0.023). For the 41 subjects in high DTC group who completed all 12 weeks of treatment, 45.5% of dutasteride treated subjects had no heaving drinking during the last month of treatment compared with 10.5% of placebo treated subjects [χ^2=6.0, p=0.014; OR = 7.1 (95% CI=1.3-38.3) NNT=3].

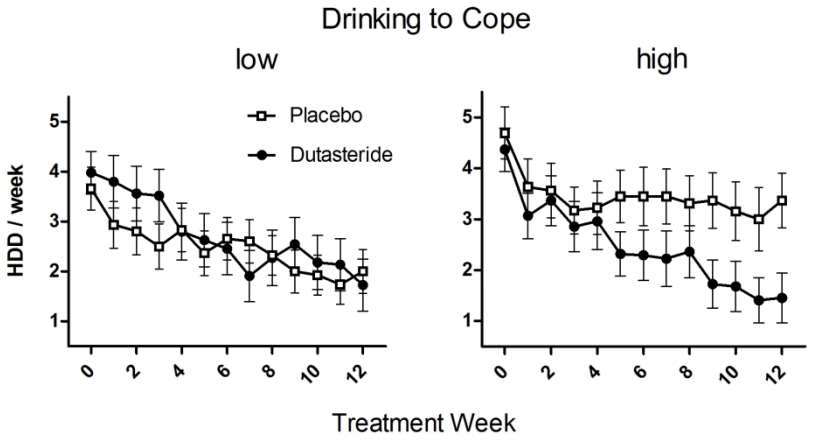

Figure 2. Mean heavy drinking days per week for dutasteride vs. placebo subjects stratified by a median split for low vs. high drinking to cope as a proportion of total drinking motives score (0-25% vs. 26-63%). Low DTC group (left) - 31 placebo and 25 dutasteride subjects; high DTC group (right) - 23 placebo and 30 dutasteride. The standard error of the mean is represented.

The high drinking to cope group had higher baseline Spielberger Anxiety Inventory scores (SAI, t= 2.6, df=107, p=.010) which were moderately correlated with DTC scores (r=.36, p<0.01). When patients were contrasted based on median baseline SAI score, there was a main effect of drug in the high but not low anxiety group for both HDD/wk (F=5.7, df=1,557, p=0.017) and SD/wk and (F=10.7, df=1,557, p=0.001) with the form of interaction similar to that illustrated in Fig 2 for high vs. low DTC score.

We did not exclude subjects with concomitant use of medications for anxiety or depression, 20% of subjects were taking such medications at baseline. Patients in the high DTC group were more likely to take medication for anxiety or depression than the low DTC group 28.3% vs. 12.5% [χ^2=4.2, p=0.04; OR = 2.7].

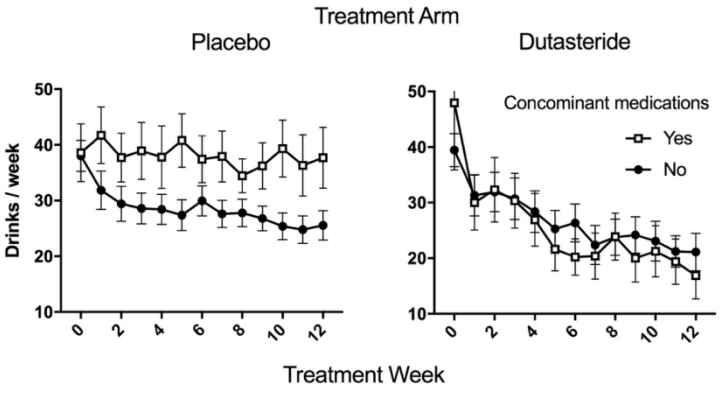

Figure 3. Mean drinks per week contrasting subjects taking or not taking concominant medications for anxiety or depression stratified by placebo (left) vs. dutasteride treatment (right). The standard error of the mean is represented.

Reductions in drinks per week among dutasteride treated subjects was not impacted by concurrent medication use for anxiety or depression (Fig 3 right), while among placebo subjects there were very limited reductions in drinking for subjects taking medication for anxiety or depression compared with placebo treated subjects without ongoing use of such medications (SD/wk F=7.8, df=1,596, p=0.005), Fig 3 left.

Summary: Results from the first study of dutasteride for AUD conducted in men indicate that dutasteride is well tolerated and significantly reduced alcohol use compared with placebo in moderate to heavy drinkers. Further, dutasteride-treated subjects with elevated baseline self-reported DTC motives and anxiety showed the largest reductions in drinking compared with placebo. Drinking to cope with negative affect and anxiety are common clinical challenges in the treatment of AUD (Smith and Randall 2012) (Menary, Kushner et al. 2011, Crum, Mojtabai et al. 2013). These results suggest that dutasteride may have particular benefit for patients with these characteristics. The associations of dutasteride response with baseline measures related to stress suggest that the effects of dutasteride to reduce drinking may include a mechanism of action involving the HPA stress response system.

The proposed study will extend these results by including both sexes and extend our analysis of the relationship of baseline drinking to cope (DTC) and anxiety by adding baseline standardized questionnaires measuring trait anxiety (STAI), early life adversity (ACES), and a perceived stress scale (PSS) which in other settings was more predictive of health care utilization than stressful life event counts (Cohen, Kamarck et al. 1983). Women are expected to have a greater likelihood of elevated DTC, ACES, trait anxiety scores (Smith and Randall 2012) which will enrich our sample in subjects potentially more responsive to dutasteride vs. pbo. We will use separate randomizations for women vs. men and include dichotomized scores for DTC and *FKBP5* risk allele carrier status in our URN randomization to balance for these potential predictors of efficacy. This study may identify easy to score pre-treatment measures such as the CDMQ, ACES, STAI, PSS and genotype that could be clinically useful for making personalized treatment recommendations regarding use of dutasteride to reduce heavy drinking.

2.C. Experimental Approach / Research Plan

2.C.1. General Design: The study will be conducted in the UCHC Clinical Research Center (CRC) clinic. Random assignment to initial treatment group and double-blind conditions will be maintained throughout the study. The study consists of two 12-week phases (**Table 1**), the first being a 12-week parallel-groups comparison of dutasteride and pbo to evaluate the safety and efficacy of dutasteride 1 mg/day in reducing the likelihood of drinking and heavy drinking in a sample of treatment-seeking men and women with AUD. In the second 12-week phase, responders in phase 1 (defined as a ≥60% reduction in SD/wk for weeks 9-12 compared with screening) will continue on their initial medication assignment, while non-responder subjects treated with placebo will cross over to dutasteride, and non-responder subjects treated with dutasteride will cross over to naltrexone. This design maintains double blind conditions in both phases 1 and 2 and is innovative. This design will: i) promote retention and recruitment, as subjects who do not respond to treatment in phase 1 will cross-over to an active FDA approved medication for AUD, ii) provide two comparisons to examine dutasteride efficacy, a between-subjects

comparison in phase 1 and a within-subjects test in phase 2 for patients treated with pbo in phase 1 and dutasteride in phase 2, iii) allow evaluation of whether reductions in drinking are maintained with ongoing treatment for phase 1 dutasteride responders, and iv) provide preliminary data on whether dutasteride non-responders show reductions in drinking when crossed over to naltrexone, an established medication for AUD with a different mechanism of action compared with dutasteride.

Three and six-month follow-up visits following the completion of the 24-week treatment phase will evaluate the durability of treatment effects, allow measurement of the degree to which dutasteride effects on 5AR inhibition have been reversed following 12- or 24-week exposures and to maintain contact with female participants to remind them of the importance of effective contraception for 6 months following treatment.

Table 1. Expected Patient Distribution for Phase 1 and 2.

Phase 1 Treatment	Phase 1 Statistical contrasts	Phase 1 Expected Tx response groups	Phase 2 Treatment	Phase 2 Statistical contrasts
Dutasteride n=95 (grp **A**)	Between-subject contrasts using GLMM Dut vs. Pbo for DVs HDD/wk and SD/wk;. Moderating effects of genotype, baseline state vs. trait anxiety, perceived stress and interaction with *FKBP5* genotype	**Dut-R** (wk 9-12 Response n=40) **Dut-NR** (wk 9-12 Non-Response n=40)	**Dut-R** dutasteride **Dut-NR** naltrexone	Within-subject interrupted time series regression using mixed models. **Dut-R:** Is dut response maintained? **Dut-NR:** Do dut NRs respond to naltrexone?
Pbo n=95 (grp **B**)		**Pbo-R** (wk 9-12 Response n=16) **Pbo-NR** (wk 9-12 Non-Response n=64)	**Pbo-R** pbo **Pbo-NR** dutasteride	**Pbo-R:** insufficient sample for statistical comparison. **Pbo-NR:** Do pbo NRs respond to Dut?

Phase 1 response ≥ 60% reduction SD/wk for wk 9-12 vs baseline (current study 49% response rate for dut vs. 20% pbo). dutasteride 1 mg/day; naltrexone 50 mg/day.

2.C.2. Patients: Drinkers who want to reduce or stop drinking will be recruited using advertisements in radio and print media, by posting/distributing recruitment materials in community settings, informational mailings to area clinicians and by referral from UConn Health medical and dental clinics in at our main campus in Farmington CT together with

satellite outpatient clinics in Canton, East Hartford, Putnam, Simsbury, Southington, Storrs, and West Hartford CT. Based on prior UConn ARC pharmacotherapy trials open to men and women (Kranzler, Tennen et al. 2009, Kranzler, Armeli et al. 2011, Kranzler, Covault et al. 2014) we anticipate that 35% of subjects will be female. Approximately 260 subjects will be enrolled (in person screening visit) with the goal of randomizing 190 to medication with 160 completing the initial 12 weeks of treatment. In the current study limited to men only, we enrolled 189 men and of these randomized 142. At least four factors will contribute to success in enhancing our recruitment in order to randomize 190 subjects in the proposed study: i) inclusion of women (35% of subjects), ii) UCONN Health has recently adopted the EPIC electronic medical record system which includes clinical trial notice pop up feature on clinicians' patient management screens with link to information about our clinical trial for patients with a clinic problem list entry of alcohol use disorder, iii) involvement of Dr. Surita Rao as a co-investigator who is the past-president and current board member of the CT Chapter of the American Society for Addiction Medicine and has agreed to send an informational letter and recruitment flyers for the study to all central CT members of ASAM, and iv) the PI's greater experience in recruitment compared with the current study which was the first clinical trial for which he served as Principal Investigator.

2.C.2.a. Temporal Sequence of Screening: Prospective participants will first undergo phone screening including the AUDIT-C three-item screener (Dawson, Grant et al. 2005) to assess key inclusion / exclusion criteria. Patients who appear to be eligible will be invited for an in-person screening. After informed consent is obtained, staff will administer several questionnaires, obtain a medical history, collect urine and blood specimens for clinical screening and for genotyping the *FKBP5* rs1360780 polymorphism to allow balanced genotype distributions in the dutasteride and pbo treatment arms. Patients will receive a physical examination by a study physician and if no exclusions are identified will be randomized to receive study medication.

2.C.2.b. Inclusion Criteria: a) men and women age 35 to 70 yo inclusive; b) have an average weekly ethanol consumption of ≥24 SD for men and ≥18 for women and at least 2 HDD/wk over the 8 weeks prior to screening [i.e., substantially in excess of non-hazardous drinking levels (Sanchez-Craig, Wilkinson et al. 1995)]; c) current DSM-5 AUD, d) Have a goal to reduce or stop drinking, e) no evidence of significant cognitive impairment; and f) for women of child-bearing potential (i.e., no hysterectomy, bilateral oophorectomy, or tubal ligation; or <2 years postmenopausal) must be non-lactating, practicing a reliable method of birth control and agree to continue such throughout the study and for 6 months following participation , and have a negative serum pregnancy test prior to initiation of treatment.

We are limiting participation to patients ≥35 yo to minimize the risk to female participants in a phase of life when pregnancy is more common (<35 yo). In our prior studies, only 5% of subjects have been younger than 35. Overall, patients for this study are anticipated to have a moderate level of AUD severity. They will be asked to affirm a

treatment goal of either stopping drinking or reducing their drinking to non-hazardous levels including no heavy drinking days (≤4 SD/day men ≤3 SD/day women).

2.C.2.c. Exclusion Criteria: Although we will not set a specific upper limit of drinks per week, we will exclude subjects with either a) history of serious alcohol withdrawal symptoms (e.g., perceptual distortions, seizures, delirium, or hallucinations), or b) subjects who on clinical examination by a physician are deemed to be too severely alcohol dependent to permit them to participate in a pbo-controlled study (e.g., evidence of serious adverse medical or psychiatric effects that are exacerbated by heavy drinking and would, for safety reasons, lead the physician to urge the patient to be totally abstinent and engage in an empirically supported treatment); other exclusions include: c) current, clinically significant physical disease, body weight >340 lbs or abnormality on the basis of medical history, physical examination, or routine laboratory evaluation, including direct bilirubin more than 2.5 times the upper limit of normal or transaminase elevations 5 times the upper limit of normal (we will not exclude patients with hypertension, diabetes, asthma or other common medical conditions, if these are adequately controlled and the patient has an ongoing relationship with a primary care provider), d) have a serious psychiatric illness on the basis of history or psychiatric examination (i.e., schizophrenia, active clinically significant mood episode of bipolar disorder or major depression, organic mental disorder, current clinically significant eating disorder, or substantial suicide or violence risk); e) have a current DSM-5 diagnosis of moderate drug use disorder (other than caffeine or nicotine dependence); f) currently taking finasteride, dutasteride, medication for treatment of AUD, or chronic use of opioid pain medication; g) are considered by the investigators to be an unsuitable candidate for an investigational drug.

2.C.3. Study Drugs:

2.C.3.a. Dutasteride is FDA approved to treat prostatic hypertrophy and is a competitive and specific inhibitor of both type I and type II steroid 5α-reductase enzymes with which it forms a stable enzyme complex with very slow dissociation. In humans, type I 5AR is present in the brain, liver, adrenal gland, and adipose tissue and is responsible for one-third of circulating DHT. Type II 5AR is present in the liver and prostate, and is responsible for two-thirds of circulating DHT. For studies of alcohol use, inhibition of type I 5AR may be of particular importance, as type I 5AR, but not type II enzyme, is present in the adult brain (Lephart, Lund et al. 2001) where local generation of neuroactive steroids is thought to occur in addition to peripherally generated neuroactive steroids. The dutasteride dose of 1 mg/day proposed for this study is expected to achieve a >90% inhibition of peripheral type II 5AR and a 60% inhibition of type 1 5AR by 4 weeks for a total reduction in DHT of ≅ 80% by 4 wks based on pharmacokinetic models (Gisleskog, Hermann et al. 1998) and consistent with our observed 80% reduction in 3α-adiol glucuronide at 6 wks in our recently completed initial study in men using this dose. Dutasteride will be purchased commercially and over encapsulated using opaque capsules by the UConn Health Research Pharmacy Service. Pbo will be formulated to match the active medication. Subjects will take one 0.5 mg capsule of dutasteride or matching pbo during the first

treatment visit (baseline study visit 2) and at home on day 2 followed by two capsules daily for either 12 or 24 weeks (depending on treatment response). Similarly, subjects transitioning from placebo or dutasteride based on phase 1 non-response will be given one capsule of medication (dutasteride 0.5 mg or naltrexone 25 mg) during their first phase 2 study visit and day 2 of phase 2 followed by two capsules daily for 12 weeks.

Dutasteride is contraindicated for use in pregnant women due to the potential effects of dutasteride in utero on the normal development of external male genitalia secondary to reduced fetal DHT (Avodart, Prescribing information 2012, GlaxoSmithKline). As noted in the inclusion criteria and in human subject protections, we will limit participation to women ≥35 who are either not sexually active with men, are practicing effective contraception or are without reproductive capacity. Female participants must have a negative serum β-HCG at study entry and will be monitored every 6 weeks during treatment using urinary HCG. Dutasteride has been safely used off label to treat alopecia (Boersma, Oranje et al. 2014, Seale, Eglini et al. 2016) in pre- and post-menopausal women in clinical practice and pre-menstrual dysphoria in a placebo controlled clinical trial (Martinez, Rubinow et al. 2016). Dr. Covault has an IND 74,222 for the study of dutasteride for AUD which includes a protocol including women.

2.C.3.b. Naltrexone is FDA approved both as an oral daily treatment (50 mg, Revia) and a long-acting depot IM formulation (Vivitrol) for the treatment of alcohol use disorder. Naltrexone has been shown to reduce heavy drinking in multiple RCTs (Maisel, Blodgett et al. 2013, Jonas, Amick et al. 2014). Naltrexone is an antagonist of the μ-opioid and κ-opioid receptors is thought to reduce alcohol craving and heavy drinking by blocking endogenous opioid induced dopamine release in response to the anticipation of drinking or use of alcohol. Naltrexone will be purchased commercially and over encapsulated using opaque capsules by the UConn Health Research Pharmacy Service. Naltrexone, dutasteride and placebo capsules will be identical in appearance. Subjects assigned to naltrexone in study phase 2 will take 1 capsule of naltrexone 25 mg on phase 2 day 1 and 2 and then 2 capsules each day containing in total 50 mg naltrexone for the remainder of phase 2. All subjects who transition to a different study medication at end of phase 1 will be required to have a negative urine test for opioids and report no opioid use for at least 5 days.

2.C.3.c. Pbo drug will consist of lactose powder formulated by the UCONN Health Research Pharmacy Service in gelatin capsules indistinguishable from the capsules containing dutasteride or naltrexone.

2.C.3.d. Medication Randomization and Drug Accountability: Urn randomization (Stout, Wirtz et al. 1994) will be used to assign subjects 1:1 to dutasteride or pbo for treatment phase 1, balancing for number of DSM5 AUD criteria (2-5 vs.>5), DTC relative to total motives score (0-25% vs. >25%), *FKBP5* genotype (CC vs. T-carrier), current smoking status, and use of medication for treatment of co-morbid psychiatric condition. Separate

randomizations will be done for women and men to ensure balance on these variables in both sex groups. At the end of phase 1, patients who have reduced drinks/week by at least 60% will continue for the second 12 wks on the originally randomized treatment taking 2 capsules per day. Subjects who have reduced drinks/wk by less than 60%, will be informed that they will be transitioning to an active study medication (either dutasteride or naltrexone), and will be interviewed to confirm they have not used opioid medication for 5 days prior which will be verified by urine testing, subjects testing positive for opioids will not be eligible for starting phase 2. For non-responder subjects in the phase 1 pbo arm, the pharmacy will begin dispensing 0.5 mg dutasteride capsules with instructions to take 1 capsule per day for 2 days, then 2 capsules daily for 12 weeks. For subjects in the initial dutasteride arm and reducing less than 60%, the pharmacy will dispense 25 mg naltrexone capsules with the same instructions of 1 capsule for days 1 and 2 followed by 2 capsules each day (50 mg naltrexone per day) to match the dutasteride capsule dosing. Medication vials including any unused medication will brought to each follow-up visit. Unused pill counts will be recorded by the study nurse at each bi-weekly visit and medication use recorded daily by patients on their drink log.

2.C.4. Study Visits:

At the screening visit, ~~the~~ patient's breath alcohol or salivary alcohol level will be measured as a surrogate for blood alcohol concentration (BAC). In order to sign the study informed consent the BAC must be <0.021. At each subsequent visit, a clinical assessment for signs of alcohol intoxication will be done by a member of the study team including unexplained drowsiness, euphoria / disinhibition or failing standard field sobriety tests (horizontal gaze nystagmus test, finger-to-nose pointing and one-leg stand). If this assessment reveals two or more positive signs of alcohol intoxication, a breath alcohol or salivary alcohol test will be done as a surrogate measure of BAC.If a subject has an estimated BAC over 0.08% (the legal limit for driving in Connecticut) they will be asked to turn their car keys over to research staff to hold until their BAC has dropped to below 0.08 and has been evaluated by a research clinic nurse or physician to assess subject safety. Intoxicated subjects who did not drive to the clinic may leave in the company of a friend or other responsible person after evaluation by clinician for safety. If a subject is impaired and refuses to cooperate with these safety procedures, the UCONN Health Police will be called 679-2121 for assistance. Additionally, at each study visit subjects will be screened for alcohol withdrawal symptoms using the Clinical Institute Withdrawal Assessment (CIWA) with a threshold score of 10 triggering evaluation by clinic physician for appropriate treatment/management.

2.C.4.a. Visit 1 (Screening Visit): After informed consent is obtained, a medical and psychiatric history will be obtained by a study nurse which will be reviewed with the participant by a study physician and any medication or study related questions reviewed.

Relevant portions of the Structured Clinical Interview for DSM-5 will be administered by a research assistant to exclude subjects with active major mental illness or current moderate to severe substance dependence other than alcohol, caffeine or tobacco. A Timeline Follow-Back (TLFB) interview will be performed to collect daily alcohol consumption for the 90 days prior to screening. Blood and urine samples will be taken for routine clinical laboratory evaluations, drug screening, DNA extraction and for measurement of the alcohol use biomarker phosphatidylethanol (PEth, which will be used as a secondary measure of drinking), the steroid metabolite 3α-diolG to monitor 5AR inhibition and ACTH and cortisol to examine for the effects of dutasteride on the ACTH/cortisol ratio. Efforts will be made to schedule individual subjects at the same time of day for each of their visits involving blood draws to reduce the within subject effects of diurnal variation in hormone levels (based on our prior studies, a majority of our subjects are anticipated to be employed with consistent times requested for study visits). Finally, subjects will be provided a stool sample collection kit and instructed on its use at home for obtaining stool samples to be returned at Visit 2. Stool samples will be collected at baseline and end of treatment phase 1 and archived at -80C for batch processing to catalog each subjects gut microbiome via DNA sequencing as part of a Center pilot project in order to contrast the gut microbiome sampled at baseline between subjects who reduce or do not reduce their drinking during phase 1 of the study. Prior reports suggest that gut colonization with pro-inflammatory microorganisms may be associated with greater difficultly in reducing drinking (Leclercq, Matamoros et al. 2014, Leclercq, de Timary et al. 2017, Leclercq, Starkel et al. 2018). We will also contrast the change in the gut microbiome comparing baseline and endpoint stool samples as a function of reduction in alcohol use. We have had good acceptance rates in pilot use of this stool collection method in other clinical studies. Subjects will be paid a nominal amount of money in consideration of their time and inconvenience for visits beyond the baseline visit (e.g., visits 3-16) as well as for completing the IVR daily calls. Total potential compensation is $620 for completing all 16 visits and all IVR calls.

2.C.4.b. Visit 2 (Baseline Visit): 3-21 days after the screening visit, eligible subjects will return for their baseline visit. Subjects will be instructed in the use of study medication and will take one capsule study medication (0.5 mg dutasteride or pbo) at the baseline visit and again on study day 2, followed by 2 capsules daily for the remainder of the phase 1 12-week treatment period (in order to match capsule number for 2 day naltrexone titration in phase 2). Finally, subjects will be trained to use a paper calendar provided by staff to record their daily drinking and use of the IVR system to record their mood, desire to drink, self-efficacy and daily drinking during weeks 1-4 and 9-12 of phase 1 and 21-24 of phase 2. We considered asking subjects to use the IVR report daily for the 168 days of treatment but considered that this would be an excessive subject burden.

Study visits beyond visit 2, may be conducted remotely by telephone if a participant is unable to come to the clinic due to illness, travel, or other valid concerns (e.g. about exposure to COVID-19) related to traveling to UConn Health. Participants will be sent a one-time use REDCap secure link via email to complete study visit surveys. In the event a

participant is unable to attend an in person scheduled visit, backup supply of medication previously provided may be used or additional medication (up to 8 weeks) will be provided at an earlier visit if inability to attend future scheduled visit is anticipated in advance. Study staff will consult with study physician regarding whether study medication should be continued if a participant reports illness as reason for a missed in person visit. All unused medications will be brought to the next in person study visit.

2.C.4.c. Bi-weekly Clinic or remote Visits 3-14: A brief Timeline Follow-Back (TLFB) interview will be performed to track participants' daily alcohol consumption and medication use since the last study visit, and a trained staff member will deliver the medical management intervention.

At the end of phase 1 treatment week 12 (visit 8) and phase 2 treatment week 24 (visit 14), subjects will complete a series of questionnaires and be interviewed by research staff concerning their alcohol consumption and alcohol-related symptomatology. For subjects who withdraw early and do not wish to continue with study visits/procedures, end-of-treatment evaluations will be administered at the time of withdrawal. Such subjects will also be invited to participate in-person or by telephone to provide drinking data for the 12-, 24-week time points in order to include this data in intent to treat analysis of the treatment phase.

2.C.4.d. Visits 15 and 16 (3- and 6-month Post-treatment Assessment): To evaluate the durability of treatment effects, patients will be invited to return to the clinic for a post-treatment assessment 3 and 6 months after completion of treatment (if unable to come in person a telephone interview will be conducted). Subjects will be contacted 6-8 weeks after end of treatment and following the 3-month follow-up visit to remind them of their follow-up appointment dates, reinforce maintaining their written drinking diary and to remind female subjects of the importance of continued use of effective contraception for 6 months following treatment. At each follow-up visit, subjects will complete self-report questionnaires and will be interviewed by the research staff. Blood samples for measurement of serum PEth, and 3α-diolG will be obtained. Subjects will be paid $50 for participating in each post treatment visit.

2.C.5. Medical Management: A study physician will meet with each subject at the beginning of treatment. The PI will consult at least weekly with study staff to monitor potential study-related side effects and will be available to personally evaluate subjects with severe or persistent adverse effects. At each treatment encounter, subjects will receive brief counseling as part of medical management, described below.

2.C.5.a. Medical Management (MM) [Adapted from (Pettinati, Weiss et al. 2004)]: The manual for this intervention was developed for use in the Combine Study (Anton, O'Malley et al. 2006) to provide a basic clinical intervention supporting medication use and monitoring of progress in reducing drinking that could be easily implemented by medically trained practitioners in non-specialty settings. A modified MM protocol that includes both abstinence or reduced drinking as an individual's stated goal will be used in the present

study. An important goal of MM is to enhance medication adherence and treatment participation through education and support.

The first MM session (study visit 2) will consist of a review of the results of the initial evaluation, to identify any medical concerns related to drinking and to reinforce subjects' treatment goal of stopping or reducing drinking to non-hazardous levels. This session will also use a self-help handout developed at the UConn ARC to encourage drinkers to self-evaluate their drinking and set goals to stop or reduce drinking. At the end of the session patients are given the opportunity to ask any questions or express any concerns that they may have about the study procedures.

Subsequent MM sessions will be conducted biweekly for the 24 weeks of active treatment. During these sessions, the study nurse will perform a review of the subject's general functioning, obtain vital signs, weight, and perform a brief assessment of the subject's drinking, monitor the subject's medication adherence, and make recommendations for the subject to follow until the next visit. For subjects who are not drinking at sensible levels, the recommendation will be made that they try different behavioral strategies for reducing drinking (e.g., spacing drinks, drinking drinks with lower alcohol content) that are outlined in the NIAAA Clinician's Guide (NIAAA 2007).

2.C.6. Assessments:

2.C.6.a. Laboratory/Medical Assessments: A physical examination, urinalysis, urine toxicology, serum bHCG (for women), CBC, and a chemistry panel (which includes electrolytes, liver enzymes [ASAT, ALAT, GGT], direct bilirubin, BUN, and creatinine) will be used to screen subjects for medical exclusion criteria. ASAT, ALAT will be repeated for subjects with elevations at baseline greater than 3x normal at weeks 6, 12, 18 and 24 (or until reduced to less than 3x normal). Weight, blood pressure and pulse will be obtained at each treatment visit. Urine will be tested every 6 weeks for drugs of abuse and HCG for women of reproductive potential. Blood will be archived for measurement of phosphatidylethanol (PEth) by a commercial testing lab as an objective measure of alcohol use. PEth is an alcohol-specific adduct catalyzed by phospholipase D from ethanol and phosphatidylcholine in membranes of red blood cells and is not affected by liver or kidney disease, age or sex. It is a sensitive and specific metabolite which is produced in direct response to use of alcohol during the past 20-30 days (Viel, Boscolo-Berto et al. 2012). PEth levels are correlated with the amount of alcohol consumed (Aradottir, Asanovska et al. 2006) and correlate better with daily diary drinking reports than carbohydrate deficient transferrin or gamma glutamyl transferase (de Bejczy, Lof et al. 2015, Walther, de Bejczy et al. 2015). Blood for PEth will be collected at screening, and weeks 6, 12, 18 and 24. Serum 3α-diolG will be measured using a commercial ELISA kit as a biochemical measure of 5AR inhibition by dutasteride. 3α-diolG is a major metabolite of testosterone and is more abundant that DHT especially in women and has been shown to decrease in parallel

with DHT following finasteride treatment in men (Rittmaster, Stoner et al. 1989, Gormley, Stoner et al. 1990) and has been used to monitor the reduction of 5AR activity in women treated with finasteride (Wong, Morris et al. 1995, Falsetti, Gambera et al. 1999). Serum testosterone, estradiol, progesterone, cortisol, ACTH and sex hormone binding globulin will be measured using commercial immunoassays to evaluate changes in these steroid hormones during treatment with dutasteride. Blood for 3α-diolG and steroid hormones will be collected at screening and weeks 6, 12, 18 and 24.

2.C.6.b. Psychological/Behavioral Assessments: The assessments listed below were chosen because they: a) are widely used assessments which will facilitate comparison of findings with prior treatment studies, b) include measures drinking motives, both trait and state anxiety, developmental adversity and perceived stress as potential predictors of treatment outcome, c) measure multiple outcome criteria, since a reduction in drinking may or may not result in improvement in other domains, and d) assess for potential change in depression or anxiety related to treatment as additional safety measures. The majority of patient report questionnaires will utilize the REDCap software package developed at Vanderbilt University. REDCap is a secure, web-based application for capturing data from participant self-reports or from staff interactions with study participants. Similarly, an online application NetSCID-5™ (Telesage) will be used by study staff to administer the structured clinical interview for DSM-5.

2.C.6.b.1. **Areas assessed only at Visit 1 (in person screening):** *a) Medical/Sociodemographic information*: Medical history, marital status, educational and occupational information. *b)* NetSCID-5™ *a web based version of the Structured Clinical Interview for DSM-5* (First, Williams et al. 2016) will be used to classify subjects according to the presence or absence of psychiatric disorders including AUD. The alcohol portion of the SCID will be administered at the 12 and 24 week (end phase 1 and B) and the 3- and 6-month follow-up visits to evaluate presence of current alcohol dependence criteria. *c) Family history of alcohol dependence:* We will use the alcohol section of the Family History Assessment Module FHAM (Rice, Reich et al. 1995) , subjects will be asked to provide information concerning thier biological relatives' history of alcohol use, however, names of family members will not be obtained. *d). Alcohol Use Disorders Identification* Test (AUDIT) (Saunders, Aasland et al. 1993) is a widely used instrument to screen for hazardous drinking, AUDIT scores will provide a measure of alcohol involvement for our study sample to allow comparison with other research samples and clinical populations. It will be administered by the study nurse during review of medical history and provides a frame for nurse engagement of subjects during medical management sessions. e*) Traumatic Events Screening Inventory (TESI)* (Ford, Grasso et al. 2013) has 18 items that assess various types of trauma that with a total of nine trauma categories (i.e., accident/illness/disaster, traumatic loss/separation, traumatic physical victimization, traumatic sexual victimization, traumatic emotional victimization, traumatic domestic violence victimization, witnessed trauma, traumatic war victimization, or other traumatic events). Subjects indicate (yes/no)

as to whether events occurred before age 6, between ages 6 and 17, above age 18 or within the past year. We previously reported an interaction of *FKBP5* genotype and trauma measured with the TESI on drinking in a large college student sample (Lieberman, Armeli et al. 2016). Presence or absence of childhood trauma will be evaluated for main and interactive effects with *FKBP5* genotype on predicting treatment outcomes; *g) Adverse Child Experiences Scale (ACES)* The ACES assesses early life stress in the form of childhood exposure to adverse experiences and a risky family environment (Felitti, Anda et al. 1998). This 17 item questionnaire probes childhood exposures including psychological abuse, physical abuse, sexual abuse, substance abuse within the family, mental illness within the family, violence toward mother, and criminal behavior in the household. Felitti et al. (Felitti, Anda et al. 1998) found that in a large sample of adults belonging to a HMO, more than half endorsed at least one category of childhood exposure. Individuals who had experienced four or more categories of childhood exposure had 4 to 12-fold increased risk for alcoholism, drug abuse, depression and risky sexual behavior. Scores for the ACES will be evaluated for main and interactive effects with the *FKBP5* genotype on predicting treatment outcomes.

2.C.6.b.2. Areas assessed daily during the active treatment period: IVR will be used to collect daily subjective ratings of alcohol-related expectancies, craving, anxiety/tension, and self-efficacy to reduce drinking, as well as drinking amounts. To reduce subject burden for daily IVR in this 24-wk study, we will use IVR to capture daily data for the first 4 study weeks and the last 4 weeks of both phase 1 and phase 2. The IVR daily drinking data will be used together with bi-weekly drinking reports to determine treatment response (60% reduction in drinks/wk) during the last 4 weeks of phase 1 to inform treatment assignment for phase 2. Daily IVR reports will also enable us to address whether study medication moderates associations between daily mood, drinking motives, self-efficacy or daily events and drinking as has been reported using IVR methods for treatment with naltrexone and topiramate (Kranzler, Armeli et al. 2004, Armeli, Feinn et al. 2006). Moderation of relationships between daily mood reports and drinking by medication will be contrasted between baseline and end of phase 1 or 2.

Table 2: Schedule of Assessments

Study Visit	V1 Screen	V2 Baseline	V 3-7	phase 2 baseline	V 9-13	V14	V15-16
Time relative to Medication		Start medication	wks 2, 4,6,8,10	wk 12 end phase 1	wks 14, 16,18,20,22	wk 24 end phase 2	3- and 6-mo follow-up
Medical History, demographics, AUDIT, SCID, FHAM, ACES, TESI, STAI-trait, Clinical screening labs, blood for DNA and research analytes Physical Exam & Clinician review of Medical History	X						

TLFB, PHQ-9, CIWA, MTR	X	X	X	X	X	X	X
Vital signs & weight	X	X	X	X	X	X	X
DMQ, AEQ, SIP	X			X		X	X
Study outcome blood samples	X		wk 6	X	wk 18	X	X
Urine drug screen, HCG (women), PACS	X		wk 6	X	wk 18	X	X
STAI-state, PSS		X					
STAI-trait, PSS				X		X	X
Daily IVR call		X	wk 1-4	wk 9-12		wk 21-24	
Side Effect Checklist (SAFTEE)		X	X	X	X	X	X
Medical Management		X	X	X	X	X	
Alcohol SCID past 1 month				X		X	X

The IVR system will use the same procedures we have used in the recently completed dutasteride study and prior UConn Health studies of topiramate (Kranzler, Armeli et al. 2016). *a) Daily drinking diary:* Every evening, as part of the IVR daily diary, patients will record their alcohol consumption as the number of standard drinks in each of three categories of alcoholic beverages: beer, wine, liquor. Patients are asked to report separately drinking from yesterday and any drinking during the current day, up until the time of the IVR report. This allows us to examine lagged associations with mood and life event triggers. *b) Daily mood:* Patients will be asked to rate as part of the daily IVR their mood using an adjective checklist. The checklist consists of 9 adjectives (Larsen and Diener 1992) with each rated on a 5-point scale (0 = "not at all" to 4 = "extremely"). Three adjectives for each of three mood state dimensions provide measures of positive mood, negative mood and activated mood. Subjects will also be asked to report their self-efficacy for managing life problems. c) *Daily Events*: Participants will be asked whether they experienced a list of nine possible daily events (3 stressful, 3 pleasant, and 3 situations where someone might drink). These measures will be used to assess the influence of positive and negative current life events on drinking. d) *Drinking motives:* Participants will be asked to respond to 3-items for each of three drinking motives as to why they drank today and yesterday; to cope, to enhance or to socialize on a 3-point scale (1= “not at all”, 2=”somewhat” and 3=”definitely).

2.C.6.b.3. Assessed at intake, end of treatment phase 1 and 2, and at 3-mo follow-up:

Psychological symptoms *The Physician’s Health Questionnaire (PHQ-9),* is a validated 9-item self-report measure of depressive symptoms with a total score of 0-27 (Ware, Kosinski et al. 1996, Kroenke, Spitzer et al. 2001). It will also be administered at each bi-weekly treatment visit. Spielberger State-Trait Anxiety Inventory (STAI), a 40-item self-report questionnaire (Spielberger 1983) containing 20-items each measuring Trait-anxiety vs. State-anxiety. The trait anxiety component will be administered at screening and the state anxiety at the baseline visit 2. The pre-treatment trait and state anxiety scores will be examined as predictors of dutasteride treatment efficacy. The trait-anxiety items will be asked again at the 12 and 24-week visits to monitor anxiety symptoms over time.

Perceived Stress Scale (PSS), a 10-item scale measuring perceived stress for the past month (Cohen, Kamarck et al. 1983). It has been reported to have better predictive value for health symptoms and health care utilization than life stress counts. Based on our current study interim results, we anticipate that similar to the STAI, the baseline PSS score may identify subjects most likely to benefit from dutasteride.

Drinking-motives, self-efficacy and alcohol problems*: Drinking Motives* will be measured with the Cooper Drinking Motives Questionnaire (DMQ); (Cooper, Russell et al. 1992, Cooper 1994)). This instrument contains 20 items with 4 drinking motives subscales: a) to cope motives (e.g., "Because it helps when you are feeling nervous or depressed"), b) conformity motives (e.g., "Because it helps me fit in"), c) enhancement motives (e.g., "Because it's fun"), and d) social motives (e.g., "Because it makes a social occasion more enjoyable"). The DMQ will be administered at baseline and for those subjects who continue to drink again at end of phase 1 and 2 treatment periods. Alcohol expectancies will be assessed with 24 items from the Alcohol Effects Questionnaire (AEQ; (George, Frone et al. 1995)) probing 4 positive expectancy subscales (social and physical pleasure, aggression and power, social expressiveness, and relaxation and tension reduction) and 1 negative subscales (cognitive/physical impairment) to explore potential changes as a result of treatment with dutasteride. The Short Inventory of Problems (SIP). The SIP is a 15-item instrument derived from the Drinker Inventory of Consequences (DrInC), to measure alcohol-related medical, psychological, social, occupational, and legal consequences (Feinn, Tennen et al. 2003). The Penn Alcohol Craving Scale (PACS) is a 5-item self-report measure that includes questions regarding the frequency, intensity, and duration of craving over the past week (Flannery, Volpicelli et al. 1999).

Integrity of the double blind*:* A Medication Questionnaire (MED-Q) will be completed by the subject at the end of phase 1 and 2 treatment periods (or at the time of treatment discontinuation for subjects who do not complete either treatment period). It includes an indication of which medication group the subject believes to have been in, their level of confidence in that assessment and the reasons for this belief.

2.C.6.b.4. Areas assessed biweekly during the active treatment period and follow up visits:

The timeline follow back (TLFB) (Sobell and Sobell 1992) will be used to estimate drinking at intake, at each biweekly study visit during the active treatment period and at the 3- and 6-month follow-up evaluation. This interview procedure will provide quantity/frequency of alcohol consumption data for each day since the last study visit. Time since onset of last menses will be collected at each treatment visit for women to examine as a co-variate for medication effects and safety monitoring for pre-menstrual women. *Medication adverse effects:* Subjects will provide reports of side effects at each bi-weekly study visit and the 3- and 6-month follow-ups using the widely used Systematic Assessment for Treatment Emergent Effects (SAFTEE) (Levine and Schooler 1986, Johnson, Ait-Daoud et al. 2005).

Measures of treatment received (MTR): All medication taken will be recorded. The study staff will also record the number of contact hours subjects have been exposed to for any treatment outside of the study that is related to their drinking to identify if this variable might need to be considered as a covariate in outcomes analysis.

2.C.7. Genotyping: Genotyping for urn randomization will be done using Cells-to-Ct assay reagent (Applied Biosystems, Inc) to allow genotyping at the *FKBP5* rs1360780 SNP directly from blood. The anticipated genotype distribution frequency based on our study of 1845 college students (Lieberman, Armeli et al. 2016) and the 1000 genomes project is CC 0.48 and T-carrier 0.52 for Caucasians and 0.37 and 0.63 for African-Americans. Reference DNA samples representing each of the three possible genotypes at rs1360780 will be included with each subject sample. Additional DNA will be purified from whole blood using the PureGene kit (GentraSystems, Minneapolis, MN) to allow confirmation of initial rapid genotyping for urn randomization using batched purified DNA samples. In view of advances in knowledge during the time of this study we anticipate that DNA will also be used to examine genotypes at other candidate markers related to alcohol use and related behaviors.

2.C.8 Exploratory microbiome analysis Leclercq et al (Leclercq, Matamoros et al. 2014, Leclercq, de Timary et al. 2017) have reported that as many as 40% of alcohol dependent subjects may harbor pro-inflammatory gut microbiota contributing to increased gut permeability which was associated with higher anxiety and alcohol craving after 3 weeks of abstinence. Our hypothesis is that participants with higher levels of pro-inflammatory gut microbes at baseline will have less success in reducing drinking. Stool samples will be collected by participants at home and transported to the CRC in a small cooler with freezer packs. Samples will be stored at -80C until batch processed. DNA will be prepared from stool samples and used for metagenomics whole genome shotgun sequencing of microbial DNA. This method allows species and strain level identification of the gut microbiome. Analysis of sequence data and comparison of strains by treatment response will be done by Dr. Yanjiao Zhou Assistant Professor of Medicine at UConn Health who is an experienced investigator in molecular characterization of human microbiomes. Correlations of the relative abundance of microbes in baseline stool samples with participant success and in reducing weekly drinking will be examined. We will also examine change in microbiome between baseline and endpoint as a function of change in drinking.

2.C.9. Data Analysis:

2.C.9.a.1. Safety: Safety will be analyzed using categorical outcomes, defined by the type and severity of adverse effects. Summary measures of adverse effects (AEs) will be developed by organ system from the SAFTEE adverse event checklist and will be compared for patients receiving dutasteride or pbo using χ^2 analysis in phase 1 and

comparing patients switched to dutasteride vs. naltrexone in phase 2. Comparisons will be conducted on 1) the proportion of patients in each of the comparison groups who report AEs, 2) the proportion of patients in each of the comparison groups who report moderate-to-severe AEs, and 3) the proportion of patients in each comparison group who discontinue treatment due to AEs. Individual AEs that occur in $\geq$ 5% of patients in either medication condition will be examined using χ^2 analysis.

2.C.9.a.2. Efficacy: Primary treatment outcomes will be defined in terms of HDD/wk and SD/wk based on TLFB reports of drinking. Reduction in these measures is related to health benefits of reduced drinking. These are the measures that are used to define non-hazardous drinking. Secondary outcomes will include proportion of days abstinent (PDA), % of subjects with no HDDs, % of subjects with non-hazardous drinking (no HDD and SD/week <15 men/<8 women) during the last 4 weeks of each treatment phase, and change in PEth at end of each treatment phase relative to baseline.

For the phase 1 comparison of dutasteride and pbo over time, efficacy analyses will be performed using generalized linear mixed (GLMM) models implemented in SPSS. GLMM incorporates within subject correlation effects important in examination of repeated measures, can incorporate multiple covariates, interactions, random and fixed effects, non-normal distributions, and is often recommended for designs such as proposed (Mallinckrodt C 2017). Medication group will be treated as a factor and treatment week as a continuous covariate. Sex, smoking status, treatment goal (stop vs. reduce drinking), and use of concurrent medication for co-morbid psychiatric conditions will also be examined as baseline between-subject covariates. Medication group, week, and the other covariates will be modeled as fixed effects, and the intercept will be modeled as random effects. For the outcome HDD/wk a binomial distribution with logit link will be used where the number of HDD during the week will be the numerator and number of observed days the denominator. For the outcome SD/wk a negative binomial distribution with log link will be used. An interaction term between medication group and the week term(s) will be used to evaluate whether the efficacy of dutasteride compared to pbo in reducing drinking varies over time. Interaction effects of sex and treatment condition will also be examined. Pretreatment drinking will be controlled using baseline TLFB drinking data as a covariate. The robustness of results will be evaluated by running the model under three different conditions: 1) modified intention to treat using all available outcome information from subjects with at least 1 post-randomization visit, 2) data from 12-week per protocol completers, and 3) multiple imputation using 10 imputed data sets with weekly drinking and baseline covariates thought predictive of the outcomes or missingness included in the imputation phase.

For aim 2, phase 2 outcomes, the within-subjects analysis will compare drinking during phase 1 against phase 2 for three groups: a) patients responsive to dutasteride in phase 1 and continuing on dutasteride for an additional 12-weeks in phase 2, to examine whether the response is maintained with continued treatment; b) phase 1 non-responders crossed over from pbo in phase 1 to dutasteride in phase 2 to provide a second contrast using an A-B design of the efficacy of dutasteride compared with pbo; and c) phase 1

dutasteride arm non-responders switched to naltrexone to determine whether naltrexone is effective in reducing drinking in dutasteride non-responders. An interrupted time series regression using mixed models will be used (Wagner, Soumerai et al. 2002, mallinckrodt and Lipkovich 2017), where in addition to a variable for week an indicator variable for phase, a second weekly variable that is sequentially coded beginning at phase 2 and the interaction of the two variables will be included in the model. The phase indicator variable will measure change when entering phase 2 and the second weekly variable will measure change in trajectory deviating from phase 1. In addition, a restricted period analysis focusing on the average of the last 4 weeks of phase 1 compared to average of the last 4 weeks of phase 2 will be conducted. This may be more sensitive if the first few weeks of each phase show limited initial response, which would dilute the effects for phase and the interaction for the interrupted regression model. For the first group, dutasteride responders, a non-inferiority test will be used where the non-inferior margin will be 20% above the drinking levels during phase 1. For the latter two groups of non-responders a superiority test will be used.

For aim 3, analysis of drinking outcomes will be repeated including baseline measures of DTC, trait anxiety, perceived stress, adverse child event count and genotype for the *FKBP5* rs1360780 SNP (CC vs. T-carrier) as additional between-subject factors together with the 2- and 3-way interactions of medication condition with DTC, SAI, PSS or ACES measures and *FKBP5* genotype. We will include both Blacks and Caucasians in the pharmacogenetics analysis as our prior study showed similar interactions of *FKBP5* genotype with life stress on drinking measures in both Black and Caucasian college students (Lieberman, Armeli et al. 2016).

2.C.9.b. Sample size considerations: For Aim 1, the proposed sample size of 160 completing the phase 1 12-week treatment (80 per arm), has 80% power to show statistical significance (α=0.05) for medium-size effects, d=0.4, such as observed in our initial RCT of dutasteride in men (d=0.38 for change in SDs/wk from baseline to last month of treatment comparing dutasteride and pbo n=91]. For Aim 2a, assuming 80% power and α=0.05 and a sample of 40 responder subjects continuing on dutasteride, the non-inferior margin limit would be an increase of 0.67 HDD/wk or 5 SDs/wk during the second 12 weeks dutasteride treatment. For Aim 2b, a sample of 64 placebo non-responders crossing over to dutasteride for phase 2 would have 90% power to detect a medium effect size for reduction in drinking in phase 2 using a within-subjects t-test. For Aim 3, using the GLMPOWER procedure and the between cell effects for the preliminary data presented above (section 2.B.2) for the 2-way interaction of drinking to cope x drug, a sample of 160 subjects in phase 1 would have 80% power to detect the magnitude of this interaction seen in the preliminary dataset.

Table 3. Timeline for recruitment and other study objectives:

Activity	Year 1	Year 2	Year 3	Year 4	Year 5

Staff training & study prep	■																		
Patient enrollment & randomizing 5/mo		■	■	■	■	■	■	■	■	■	■	■	■	■	■				
3- and 6-month follow-up								■	■	■	■	■	■	■	■	■	■	■	
Data entry & cleaning			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Data analysis & Report writing													■	■	■	■	■	■	■

Section 3. PROTECTION OF HUMAN SUBJECTS

3.A Risks to Human Subjects

3.A.1 Patient population: Outpatient male and female problem drinkers identified through advertisements and referral from UConn Health clinics, area mental health clinics or area providers will be randomized to study medication. We anticipate enrolling 260 subjects for screening visits in order to randomize 190 subjects to medication with a goal of 160 subjects completing the phase 1 12 weeks of study medication. Patients must be heavy drinkers (ages 35-70) who affirm a desire to stop or reduce their drinking to non-hazardous levels. Research subjects will all be in good physical health who are competent to provide consent. Subjects will be paid a nominal amount of money in consideration of their time and inconvenience for visits beyond the baseline visit (e.g. visit 3-16) as well as for completing the IVR daily calls. Total potential compensation is $620 for completing all 16 visits and IVR calls [$20/visit 3-14 paid at 6, 12, 18 and 24 weeks as well as $50 for attending the 3- and 6-month follow up visits 15-16; IVR daily phone calls weeks 1-4, 9-12, and 21-24: $2 per completed phone call plus $6 for each week where all calls are completed during phase 1 (up to $20/wk) and $3 per completed phone call plus $9 for each week where all calls are completed during phase 2 weeks 21-24 (up to $30/wk).

TABLE 2: Schedule of subject payments:

Visit 5, 6 wks, midpoint phase 1	$60
Visit 8, 12 wks, endpoint phase 1	$60
Visit 11, 18 wks, midpoint phase 2	$60
Visit 14, 24 wks, endpoint phase 2	$60
Visit 15 and 16, 3- and 6-month follow-up	$50 each
IVR	Up to $280
Maximum Total compensation for all visits and IVR phone calls	**$620**

Recruitment and informed consent procedures: Patients recruitment will use IRB-approved recruitment materials, which advertise for regular or daily drinkers who want to reduce or stop their drinking. Distribution methods will include: informational brochures in UCONN Health and affiliated primary care and dental clinics; informational mailings to area clinics; advertisements in local media (including text ads in newspapers; radio ads; web ads and web postings on community message boards); through broadcast email messages at institutions (such as UCONN Health, community agencies, local college campuses, etc.) that offer that type of service; by posting/distributing recruitment materials in community settings with public posting areas or other means of providing community access to materials (such as hospitals, town halls, public libraries, YMCA, health

fairs/organizations). A partial waiver of consent and HIPAA Authorization will be obtained from the IRB to allow for preliminary phone screening for calls initiated by potential patients. Those individuals deemed eligible for in-person screening will sign a HIPAA Authorization and study consent form at their first visit. During the in-person screening visit each patient will receive an explanation of the study protocol, its risks, potential benefits, and alternative treatment by a study staff member. Following resolution of any questions, patients who appear to understand the nature of the study and consent will be asked to sign the study consent form. An entire copy of the informed consent form will be given to each patient. Because we will be recruiting patients from throughout the Greater Hartford area, including outreach to the minority communities in the area, we anticipate that approximately 10% of patients enrolled in the study will be African-American and 8% will be Latino.

3.A.2 Sources of Research materials: Research material will include information obtained from patients. Other data will be obtained by physical examination, clinical and research laboratory evaluation, and data from observation of patients by study staff. All data will be obtained exclusively for research purposes and will be at no cost to patients. All research data and biological specimens will be stored in coded fashion without direct identifiable information. Personally identifiable information will be stored in separate secure files. Links between study IDs and personal information will be destroyed following data verification and cleaning to generate a de-identified dataset.

3.A.3 Potential risks:

General Procedures: There is some risk that patients will be identified as participants in a study of treatment for heavy drinking or that the clinical assessments will adversely affect patients' well-being.

Counseling: Medical management brief counseling has been used safely with alcohol-dependent patients in the COMBINE Study and in prior clinical trials at the UConn ARC. Psychological risks are minimal and not different from those of equivalent non-study treatments.

Medications:

Dutasteride is not reinforcing and is therefore not a drug of abuse. There are few adverse effects associated with dutasteride use (Hirshburg, Kelsey et al. 2016). Based on extensive clinical studies in men, dutasteride is well tolerated. In a series of three 2-year long treatment trials including 4,300 men aged 47-94 years (mean = 66 years), a 0.5 mg daily dose of dutasteride for treatment of enlarged prostate resulted in the following adverse effects compared with pbo: impotence (4.7% vs. 1.7%), decreased sex drive (3.0% vs. 1.4%), problems with ejaculation (1.4% vs. 0.5%), and enlargement of breast tissue (0.5% vs. 0.2%). 4% of dutasteride and 3% of pbo patients ended treatment due to

a side effect concern. In other clinical studies, daily doses of 5 mg (i.e., 5 times the daily in the proposed study for alcohol problems) were administered to 60 men for 6 months with no adverse effects beyond those seen at the more commonly used daily dose of 0.5 mg (Avodart, Prescribing information 2012, GlaxoSmithKline). Depression has been reported as a potential side effect of the 5AR inhibitor finasteride in several small retrospective case series (Hirshburg, Kelsey et al. 2016). In the only prospective study examining mood in 128 men treated with finasteride for alopecia, the Beck Depression Inventory (BDI) score increased minimally from 12.11 to 12.80 after 2 months treatment (Rahimi-Ardabili, Pourandarjani et al. 2006). In our current study of dutasteride in men we observed a decrease in BDI scores over the 12-week study period in both dutasteride and placebo arms. A recent large retrospective study of 90,000 men who initiated treatment with a 5α-reductase inhibitor (finasteride or dutasteride) during the period 2003-2013 and matched controls found no increased risk of suicide associated with medication but an increased risk of self-harm events (18 per 10,000 exposed vs. 14 per 10,000) and incident depression (194 per 10,000 exposed vs. 137 per 10,000) during the initial 18 months of treatment (Welk, McArthur et al. 2017). In view of these reports of the potential for 5α-reductase inhibitors to increase depressive symptoms, we will use the physician's health questionnaire (PHQ-9) to screen for clinical depression at every study visit. The PHQ-9 is a validated 9-item self-report measure of depressive (Ware, Kosinski et al. 1996, Kroenke, Spitzer et al. 2001), a response of 1 or greater on item 9 related to suicidal thoughts will trigger a clinical evaluation by study physician or nurse regarding safety.

A large treatment trial involving over 6,000 men, "Reduction by Dutasteride of Prostate Cancer Events (REDUCE)" evaluated the daily use of dutasteride 0.5 mg versus pbo for 4 years to examine the effects of long-term treatment with dutasteride on the risk of prostate cancer in men over 50 years of age (Andriole, Bostwick et al. 2010). The trials demonstrated an overall reduction in prostate cancer diagnosis with dutasteride compared with pbo treatment (20% vs. 25% with pbo) but an increased incidence of high-grade (Gleason score 8-10) prostate cancer (1% for dutasteride vs. 0.5% for pbo) after 4 years. The increased incidence of high-grade cancer was not observed after 2 years exposure (0.5% for dutasteride vs. 0.5% for pbo). Long-term treatment with dutasteride may increase the risk for the development of high-grade prostate cancer. The short-term use of dutasteride in this study of alcohol use is not expected to alter participants' risk of prostate cancer.

Dutasteride (and finasteride) is <u>contraindicated for use by pregnant women</u> due to the potential risk of a specific birth defect (reduced size of male external genitalia and potential for hypospadias) (Avodart, Prescribing information 2011, GlaxoSmithKline). There is <u>no known risk to non-pregnant women</u>. The 5α-reductase inhibitors finasteride and dutasteride have been used off-label in clinical practice for the long term treatment of alopecia in women without serious side effects (Boersma, Oranje et al. 2014, Hirshburg, Kelsey et al. 2016, Seale, Eglini et al. 2016). Side effects of 5AR inhibitors in women have

been reported to include headache, gastrointestinal discomfort and decreased libido in uncontrolled retrospective reports (Hirshburg, Kelsey et al. 2016). In a long-term placebo controlled study involving 137 women ages 41-60 yo who were treated for 1 year with finasteride or placebo for alopecia there were no statistically significant differences in rates of side effects for finasteride vs. placebo (Price, Roberts et al. 2000). Dutasteride was well tolerated and effective in reducing pre-menstrual dysphoria in a clinical research study in which women were treated daily with 2.5 mg of dutasteride for 1 month (Martinez, Rubinow et al. 2016). Women of reproductive potential should practice effective contraception while using dutasteride and for 6 months following discontinuation of medication to prevent unintended exposure to a male fetus consistent with package label recommending that men refrain from donating blood for 6 months following use of dutasteride.

While it is theoretically possible to expose a pregnant woman to dutasteride via semen, exposure of pregnant non-human primates intravenously with16x the potential exposure from 5 ml of semen daily (assuming 100% absorption of dutasteride) was without adverse effect on the offspring (Avodart, Prescribing information 2011, GlaxoSmithKline). No precautions are listed in the package insert regarding exposure of female partners to semen of men taking dutasteride. As recommended in the package insert, subjects will be warned to not donate blood products for 6 months following study treatment to prevent unintended exposure to dutasteride to pregnant women.

Naltrexone is FDA approved for the treatment of alcohol dependence as well as for opioid dependence. Naltrexone has also been shown to reduce heavy drinking in multiple RCTs (Maisel, Blodgett et al. 2013, Jonas, Amick et al. 2014). Naltrexone is an antagonist of the μ-opioid and κ-opioid receptors is thought to reduce alcohol craving and heavy drinking by blocking the endogenous opioid system and thereby reducing dopamine release in response to the anticipation of or use of alcohol. Naltrexone has no abuse potential. In subjects with dependence on opioids who have recently used opiates naltrexone will precipitate withdrawal symptoms. The most common side effects of naltrexone in a large open label safety study (Croop, Faulkner et al. 1997) in 570 subjects with alcoholism (Revia, Prescribing information 2013, Barr Pharmaceuticals) were: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%) insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%). A prior FDA black box warning related to possible hepatotoxicity based on naltrexone use at 300 mg / day for obesity has subsequently been removed based on extensive experience with naltrexone 50-100 mg/day for alcohol dependence. Naltrexone is a pregnancy class C medication (animal data suggest teratogenic potential, but no human data available). To be eligible for participating in this study women of reproductive potential will be required to agree to use effective contraceptive practices.

Interaction of Medications and Alcohol: Neither dutasteride or naltrexone produce clinically significant additive interactions with alcohol on CNS depressant effects. Dutasteride and naltrexone are both safe in the setting of ongoing alcohol use.

Blood and Urine Collection: These procedures are performed in large measure for baseline screening to safeguard that patients with untreated medical conditions are not enrolled and at subsequent visits to monitor medication safety, document urine drug use screening and verify absence of pregnancy. Additional bloods are drawn for research measures of alcohol use and dutasteride effects. These procedures should add no risks other than those normally associated with these procedures, e.g., pain and bruising as a consequence of venipuncture.

Rating Scales and Questionnaires: These are non-invasive and add no special risk, although they do cover sensitive areas. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience indicates that these measures are acceptable to patients. Careful efforts to maintain confidentiality have been effective in our previous research and will be continued.

Genetic Testing. The principal risk of genetic testing is the potential for breach of confidentiality, with information concerning the patient's genetic risk for disease becoming known. Such information, if available to the patient, could cause distress and if available to health or life insurers could adversely affect the patient's access to insurance or its benefits. To guard against these risks, patients will not be provided with genetic test results and confidentiality will be closely protected as described below. At the conclusion of the study, links between personal identifiers and the study ID associated with genetic test results and DNA / biological samples will be destroyed to generate de-identified samples and datasets. Given the small likelihood of breach of confidentiality (NB: in over 15 years of genetic research by our ARC research group, we are not aware of a single instance of such a breach), the potential benefits accruing to the research (namely, a greater understanding of the genetic basis of alcohol use disorders and related psychiatric conditions and potentially of the genetic moderators of the response to treatment with dutasteride), and the complex nature of the disorders (limiting the impact that knowledge of any single genetic variant may have on disease risk), the potential benefit-to-risk ratio is favorable.

3.B Protection Against Risks

3.B.1. Procedures to minimize potential risks: Inclusion/ criteria and the use of experienced research assistants in initial screening and review of phone screens with study investigator(s) will minimize acceptance of patients with either insufficient or currently highly hazardous alcohol use into the study. Careful pre-treatment laboratory testing and evaluation by trained, experienced staff will minimize the risk of including

individuals with contraindicated medical and/or psychiatric conditions. Experienced phlebotomists will minimize venipuncture risk. During treatment, patients' substance use and medical and psychiatric status will be closely monitored. Patients with breath or salivary alcohol levels over the legal driving limit or clinical evidence of intoxication will be examined by a study physician and monitored until no longer intoxicated, or referred for appropriate treatment, as clinically appropriate.

Identifying subjects who are inappropriate for study entry because of current alcohol withdrawal: Subjects with prominent signs of physical dependence, and/or medical comorbidities such that study physicians feel they should consider immediate detoxification, will be referred for medical detoxification in a normal treatment setting. The Clinical Institute Withdrawal Assessment (CIWA-Ar) will be used to facilitate assessment of withdrawal, and decisions regarding appropriateness for study entry with respect to physical dependence will be made based on the judgment of study physicians using the CIWA-Ar score of 10 for an approximate cutoff level. All our study physicians have extensive experience in assessing and triaging patients with alcohol withdrawal. Subjects that need detoxification will be referred for detoxification, and may be eligible to begin the study following successful completion of detoxification.

Medication risks: Frequent contact will help identify patients with adverse treatment effects. Patients will be given a card identifying themselves as participants in a study involving dutasteride or naltrexone, and containing the contact numbers of the PI and study nurse. The medication blind will be broken if necessary for emergency assessment or treatment. For example, if the PI determines that an adverse event is serious, unexpected, possibly related to the study drug, and medical intervention is needed, the PI will request from research pharmacy the medication assignment for the subject so that the patient can receive proper treatment. Adverse medication effects will be systematically evaluated and recorded. If serious, patients will be withdrawn from the study and given appropriate treatment and/or referral.

Study staff may request that pharmacy provide medication assignment after completing the 6 month follow-up or if information needed by patient for clinical discussion with their physician, it may requested after completing medication phase of study.

Procedures to minimize potential exposure of pregnant women to active study medication (dutasteride or naltrexone) include 1) excluding subjects younger than 35 who may have a greater likelihood of considering pregnancy after starting the study and would need to avoid pregnancy for 6 months following treatment with dutasteride, 2) inclusion requirement of a negative serum bHCG at screening together with monitoring of urine HCG during the 24-week treatment, 3) review of teratogenic risks by study physician with female subjects, 4) agreement by women of reproductive potential to use effective contraception during the study and for 6 months following completion of medication use, 5) monthly contact by study nurse during 6 month follow-up to remind women of importance

of effective contraception. If a patient reports being pregnant or tests positive, she will be immediately withdrawn from study medication treatment, referred for obstetric evaluation, informed as to the study medication she had taken and advised to discontinue drinking alcohol.

Confidentiality: To avoid breach of confidentiality, patients' names will appear only on a consent form, a telephone screening form, the study nurses visit contact information sheet and a "key" form kept by study staff in a locked cabinet. All forms that contain identifying information will be kept double locked (i.e., in a locked cabinet, in a locked room) to maintain their security. All study data forms will contain only the patient's unique study identification number. Prior to final study closure, any links between personal identifiers and each subject's unique study ID will be deleted to generate a de-identified dataset. Patient visits will be scheduled by study staff and no information about the patient will be provided to anyone outside the study team (except in emergencies as defined above) in person or by telephone, except as required by law. The study will be conducted in an outpatient clinic in which treatment is provided to patients who have a variety of problems, not limited to substance abuse. To further help protect participant privacy, a Certificate of Confidentiality from the National Institutes of Health will be in force for this study. This certificate will protect the investigator and immediate study staff from being forced to release any research data that would identify a participant in this study, even under a court order or subpoena.

Alternative Treatments: The alternative procedures available are counseling by other clinicians, self-help groups such as Alcoholics Anonymous, or more intensive treatment for heavy drinking, including treatment with oral or long-acting injectable naltrexone, disulfiram, or acamprosate, which are FDA-approved medications widely available for treatment of AD. Subjects requesting additional treatment for alcohol problems following completion of the study protocol or withdrawal from the study will be referred to local treatment centers.

3.B.2. Potential benefits to patients and society: Benefits to patients include careful evaluation of their medical and psychiatric status and alcohol use. Benefits to participants also include the potential for reduction in their alcohol consumption with associated improvements in their physical and psychological health, functioning at work and in their family/relationships. Benefits to society include a potential improvement in the effectiveness of treatment for problem drinking, which may reduce the personal and societal burdens associated with heavy drinking. In addition, clinicians and scientists may better understand the effects of dutasteride to reduce alcohol consumption. An improved understanding of phenotypic and genetic predictors and/or moderators of dutasteride response will offer the potential for individualized treatment and enhanced the clinical utility of dutasteride for alcohol use problems.

3.B.3. Importance of Knowledge to be Gained: Alcohol dependence has a major impact on society, families and individuals affected. AUD remains a major health concern, additional treatment options are needed. Results from our recently completed first study of dutasteride for reducing alcohol use indicate is well tolerated and may represent a very effective treatment options especially for subjects who drink to cope with negative emotions. The proposed study seeks to better identify predictors of efficacy to potentially advance medication treatment match for alcohol use treatment.

3.B.4. Comparison of risks and anticipated benefits to patients and society: The risks associated with the study counseling are minimal. Although the study medication presents some risk, dutasteride has been shown to be safe when administered for benign prostatic hypertrophy for long periods of time (years) in men and in more limited off-label treatments of women for alopecia for up to 3 years. Naltrexone is widely prescribed for treatment of alcohol use disorders in men and women with an excellent safety record. The potential risks of these treatments are low compared to the risk incurred by individuals who continue to drink heavily. The study design provides ongoing bi-weekly monitoring and support for reducing alcohol use such that placebo subjects may benefit from contact with study staff. Placebo non-responders will also be transitioned after 12-weeks to the active study medication providing potential additional benefit. In view of the potential for advancing treatment options for future patients and potential benefit to participants for reducing drinking, the risk/benefit ratio appears favorable for the proposed treatments.

3.C Data and Safety Monitoring Plan (DSMP):

The DSMP is established to ensure the safety of research participants and the integrity of the study data. Dr. Jonathan Covault, M.D., the principal investigator of this project [or in his absence or one of the other study physicians – Dr. Oncken or Rao], will be charged with the duty of determining the severity rating of adverse events. The study staff (P.I., co-investigators, clinical research assistants) are responsible for collecting and recording all clinical data. As these results are collected, any toxicities and adverse events will be identified, graded for severity and assigned causality, reported to the required entities, and compiled for periodic review. Dr. Covault or one of the other study investigator/physicians will review with study staff on a weekly basis the treatment status and any side effects for active study patients and the outcome of AEs and SAEs over time and need for intervention. Dr. Covault and study staff will meet on a semi-annual basis to review summary information regarding patient flow in the study, reasons for dropout and adverse events. This summary information will then be sent to the study's Data and Safety Monitoring Board (DSMB) for review.

AE monitoring. The study nurse will use the SAFTEE instrument to screen for adverse events at each treatment visit. The P.I. will evaluate every moderate or severe adverse event and determine whether it affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent form are required. The principal

investigator (and, in his absence, physician co-investigators) will differentiate serious from non-serious adverse events.
A Serious Adverse Events Monitoring Form will be used by study staff to provide information about all serious adverse events (expected and unexpected including not study related), how they were handled, and their potential relationship to study participation and a sign-off by appropriate supervisory personnel. Patients who experience a significant psychiatric or medical problem requiring an overnight hospitalization at an acute care facility will be considered to have experienced an SAE. Serious Adverse Events also include adverse events that result in death, a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect.

Serious adverse events (SAEs) and other serious unanticipated events that are possibly related to the study interventions will be reported within 48 hours of study team knowledge of the SAE to the 1) UCHC IRB / Office of the Vice President for Research, 2) the study DSMB, and 3) the NIAAA project officer. All other SAEs, unanticipated events and non-serious adverse events (AEs) during the treatment will be reported to the UCHC IRB, as well as to the NIAAA on an annual basis. SAEs, AEs, and unanticipated problems will be managed consistent with UConn Health IRB guidelines.
Other adverse events will be monitored during study visits or phone calls with participants and reviewed weekly at study staff meeting. An ongoing database of adverse events will be maintained by the study staff. Aggregate data on reports of adverse events will be provided to the DSMB members on a semi-annual basis as part of their semi-annual review with the study staff and PI of data and patient safety monitoring. The following information will be considered in the periodic safety report:

- Number of patients who have completed the study.
- Dropout rates and reasons for the dropouts.
- Summary of adverse events.
- Any other relevant information

The annual report to the NIAAA program officer will include

- Confirmation of adherence to the data and safety monitoring plan;
- Summary of all AEs;
- Summary of any data and safety monitoring issues that occurred since the previous reporting period;
- Description of any changes in the research protocol or the data and safety monitoring plan that potentially affect risk;
- Summary of all new IRB approvals during the report period.

Any patients thought to be at risk from drinking or psychiatric or medical disorders during treatment or the follow-up period will be referred to services at UCONN Health or to other local health service providers.

Data Monitoring. Data entry will occur at the time of visit via REDCap directly by staff or study subjects (with supervision by staff). Other data not entered at time of visit will be doubly entered via REDCap feature to assure accuracy of entry. All study staff involved in data entry are blind to treatment condition. The PI will have primary responsibility for data accuracy and compliance with protocol.

A Data Safety and Monitoring Board (DSMB) for the study will be established prior to enrollment of patients. This committee will be asked to review semi-annually study data regarding enrollment, safety and adverse events. The committee may make recommendations for early stoppage of the trial based on review of study data. DSMB members will be provided with semi-annual reports to include data that inform progress of the study, including recruitment data, and adverse events data. These data will be used to decide whether to 1) continue recruitment as planned, 2) continue with a protocol amendment, or 3) stop recruitment pending investigation. The DSMB will typically hold meetings electronically or by conference call.

Study suspension / stopping. A decision to discontinue the study will be based primarily on consideration by the DSMB of study related serious adverse events (SAE's). DSMB members will receive a copy of the Serious Adverse Events Monitoring Form within 48 hours of study team knowledge of the SAE, at which point DSMB members will make one of two recommendations: 1) continue recruitment and treatment as planned; 2) schedule a formal meeting within one week to determine if the study should: a) continue study unchanged; b) continue recruitment after a protocol amendment; or c) stop recruiting and if appropriate treatment pending further investigation.

If safety concerns warrant, upon request from DSMB members the pharmacy will provide un-blinding information regarding drug assignment.

If it has been determined, for any reason, that the study should be suspended, we will discontinue enrollment of new patients, while continuing the treatment and monitoring of patients already enrolled in the study, unless to do so would create a risk that is not justified by any potential benefit to patients.

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