April 10, 2017 (Version 7)

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Project Title: Dutasteride treatment for the reduction of heavy drinking.

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Abstract

FDA approved pharmacotherapy options for alcohol use disorders remain limited, with only three currently approved compounds (disulfiram, naltrexone and acamprosate). Recent studies highlight the potential for medications used for the treatment of other indications to be examined for the treatment of alcohol use disorders. Study of additional agents, particularly those that act through novel mechanisms, is needed to expand the range of pharmacotherapy options for alcohol use problems. Extensive preclinical studies indicate that neuroactive steroids medicate important effects of alcohol and support the examination of neuroactive steroid modulators as treatment options for alcohol use problems. Dutasteride, a widely prescribed medication for benign prostatic hypertrophy, blocks a key step in the production of neuroactive steroids and represents a promising candidate for treatment of alcohol use disorders. This study will use a randomized placebo controlled design to examine the safety and efficacy of dutasteride to reduce drinking among a sample of 160 men with hazardous levels of alcohol use. It will additionally examine the potential moderation of dutasteride treatment effects by a common missense polymorphism in a neuroactive steroid biosynthetic enzyme (3αHSD type 2; aka 17βHSD type 5) that we have previously reported to be associated with alcohol dependence. Identification of genetic predictors of medication response offers the potential for matching alcohol treatment medications with those most likely to respond.

Specific Aims.

Alcohol has multiple biological effects on the nervous system which each represent potential targets for pharmacotherapy of alcohol use disorders. Animal studies indicate that alcohol induced generation of $GABA_A$ receptor neuroactive steroid agonists mediate several of alcohol's effects. Pharmacologic blockade of neuroactive steroid production has been reported to reduce alcohol intake in animal models. Dutasteride, a widely used medication to treat benign prostatic hypertrophy is an irreversible inhibitor of 5-alpha reductase (5AR) enzymes required for the production of neuroactive steroids, and thus has potential as a pharmacologic treatment for alcohol use disorders in humans. In a recently completed placebo controlled study in humans of the effects of a single 4 mg dose of dutasteride given 2-4 days prior to a moderate dose of alcohol (0.8 gr/kg body weight) we found that while dutasteride has limited effects on subjective responses to a standard battery of alcohol effect questionnaires, it produced a significant reduction in drinking during the first two weeks following dutasteride, but not placebo medication treatments for subjects with a history of moderate drinking. The proposed study will extend these findings by examining the safety and efficacy of dutasteride for alcohol use disorders in human subjects by conducting a 12-week randomized placebo controlled trial of dutasteride for the reduction of alcohol use in male problem drinkers.

Aim 1. To examine the safety and efficacy of dutasteride in helping problem drinkers to reduce or stop drinking. 160 men with hazardous levels of alcohol use (≥24 standard drinks / week) will be randomly assigned to treatment with either dutasteride or placebo for 12-weeks. Alcohol use will be reported daily via an interactive voice response system. Biological markers (gamma glutamyl transferase, carbohydrate deficient transferin) will be used as secondary measures of change in alcohol use and a serum neuroactive steroid metabolite 3α-androstanediol glucuronide will be used to monitor inhibition of 5α-reductase enzyme activity by dutasteride. We hypothesize that 1 mg / day dutasteride will be well tolerated by heavy drinkers, will produce ≥85% reduction in serum markers of 5α-reductase enzyme activity and that compared with placebo will result in a greater reduction in the number of heavy drinking days and drinks per week.

Aim 2. To examine the durability of effects of dutasteride treatment on drinking and heavy drinking during a six-month post-treatment follow-up. Dutasteride elimination kinetics have a saturable component such that following weeks of daily dosing the elimination half-life of dutasteride gradually increases producing a delayed (weeks) recovery of 5AR activity. We hypothesize that reductions in drinking and heavy drinking during the treatment period will persist to a greater degree in dutasteride vs. placebo treated patients.

Aim 3. To examine whether treatment response is moderated by a common genetic variation, H5Q, in the neuroactive steroid biosynthetic enzyme 3α-hydroxysteroid dehydrogenase gene *AKR1C3* that has been associated with alcohol dependence. *AKR1C3* genotype will be included among urn randomization variables for assignment to drug vs. placebo groups. We hypothesize that dutasteride treatment will result in greater reductions in drinking for subjects who are homozygous for the *AKR1C3* alcohol risk allele (38% of subjects) compared with protective allele carriers.

Aim 4. To examine the potential effects of dutasteride on the relations among daily mood and daily events on drinking and heavy drinking, and the potential effects of dutasteride on daily reports of alcohol subjective effects to identify potential intermediate effects of dutasteride on treatment outcomes. We hypothesize that within-person associations between daily mood or daily events and drinking and heavy drinking will be moderated by dutasteride.

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Research Strategy

A. Significance.

Alcohol use disorders are highly prevalent, frequently chronic and have significant adverse effects on the health and quality of life of alcoholic individuals and their families. Recent large scale household surveys indicate that of US adults who use alcohol, 5% meet criteria for alcohol dependence while an additional 20% of drinkers could be considered problem drinkers who meet at least one criterion for an alcohol use disorder (McBride et al. 2009). Many if not most problem drinkers do not seek treatment and are often more interested in reducing rather than stopping drinking. Although problem drinkers can be identified using brief screening tools in primary care settings, primary care providers are often hesitant to intervene using psychological treatments for problem drinkers and may be more willing to provide medical therapies for alcohol use disorders. Pharmacotherapy options for alcohol use disorders remain limited, with only three currently FDA approved compounds (disulfiram, naltrexone and acamprosate). Recent studies highlight the potential for medications approved for the treatment of other indications (e.g. topiramate, ondansetron, zonisamide, baclofen) to be applied to treatment of alcohol use disorders [reviewed in (Edwards et al. 2011)]. Study of additional agents, particularly those that act through novel mechanisms, is needed to expand the range of pharmacotherapy options for alcohol use problems. The neuroactive steroid system represents such a novel mechanism, and dutasteride a widely prescribed medication that blocks a key step in the production of neuroactive steroids represents a promising candidate for treatment of alcohol use disorders. This study will examine the safety and efficacy of dutasteride to reduce drinking among heavy drinkers. It will additionally examine the potential moderation of treatment effects of dutasteride by a common missense polymorphism in a neuroactive steroid biosynthetic enzyme which we have shown to be associated with alcohol dependence (Milivojevic et al. 2011). Identification of genetic predictors of medication response offers the potential for matching alcohol treatment medications with those more likely to respond (Kranzler and Edenberg 2010; Johnson et al. 2011; Kranzler et al. 2011). While this study will examine only men, as dutasteride is currently not FDA approved for use in women due to the potential for adverse effects on fetal development of male external genitalia, men represent an important target population as alcohol use disorders are significantly more common in men than women.

B. Innovation.

The primary innovation of the proposed study is the examination of a novel therapeutic mechanism, inhibition of 5α-reduced neuroactive steroid production, to reduce alcohol use among heavy drinkers using a currently approved and well tolerated medication, dutasteride. Dutasteride is somewhat unique in having a long-half life following repeated administration providing a natural prolonged effect and slow self taper following end of treatment. Additional innovative components include examination of a strong candidate genetic polymorphism for moderation of dutasteride effect and use of daily self reports of mood, life events, alcohol effects and alcohol use via an interactive voice response system (IVR) to allow examination of moderating effects of dutasteride on relationships between mood, daily events and drinking as well as explore potential effects of dutasteride on subjective alcohol effects in a natural setting.

Neuroactive steroids and alcohol effects.

An extensive body of pre-clinical studies support the hypothesis that endogenous neuroactive steroids produced in response to alcohol mediate some of the behavioral and electrophysiological effects of alcohol [reviewed in (Kumar et al. 2009)]. 5α reduced 3α-hydroxy-pregnane and 3α-hydroxy-androstane neuroactive steroids are endogenous, highly potent (i.e., active at nanomolar concentrations), positive allosteric modulators of $GABA_A$ receptor function (Paul and Purdy 1992) that are produced both peripherally and in the brain. They increase the frequency and the duration of the open state of GABA-gated chloride channels (Belelli et al. 2005), contributing to neuroactive steroid's anticonvulsant (Belelli et al. 1989; Reddy 2004), antinociceptive (Nadeson and Goodchild 2001), antidepressant (Khisti et al. 2000; Uzunova et al. 2006) and anxiolytic (Bitran et al. 1991; Wieland et al. 1991; Akwa et al. 1999) properties.

In rat models, alcohol increases levels of neuroactive steroids in plasma and brain of intact animals and in brain slice preparations (Barbaccia et al. 1999; Morrow et al. 1999; VanDoren et al. 2000; O'Dell et al. 2004; Sanna et al. 2004). Blockade of ethanol-induced increases in neuroactive steroids in rats using the 5AR inhibitor finasteride attenuates several behavioral effects of alcohol (VanDoren et al. 2000; Hirani et al. 2002; Hirani et al. 2005) and blocks effects of alcohol on $GABA_A$ currents in brain slice preparations (Sanna 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 et al. 2005) or the synthetic neurosteroid agonist ganaxolone (Besheer 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 et al. 2005). Additionally, blockade of neuroactive steroid production by the 5AR inhibitor finasteride attenuates acquisition of alcohol preference in mice (Ford et al. 2008) and reduces the self-administration of alcohol in mice previously training to self-administer ethanol (Ford et al. 2005) as well as in naïve mice (Ramaker et al. 2011). Together these results from pre-clinical studies suggest that alcohol related changes in neuroactive steroid levels or patterns of metabolism contribute to the reinforcing aspects of alcohol in self-administration paradigms and 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 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 intoxication (Holdstock et al. 2006; Pierucci-Lagha et al. 2006; Porcu et al. 2009). Recently (see preliminary studies) we have reported 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 AD (Milivojevic et al. 2011).

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 but in humans, finasteride at typical clinical doses blocks only type II 5AR, the isoenzyme of 5AR most abundant in prostate and skin but absent in adult brain. Dutasteride, a second FDA approved 5AR inhibitor for treatment of prostatic hyperplasia, irreversibly inhibits of both type I (brain, adrenal and liver) and type II (liver, skin and prostate) 5AR enzymes at clinically relevant dosages, leading to a greater reduction in 5α-dihydrotestosterone (DHT) levels compared with finasteride without suppressing testosterone (Clark et al. 2004). This broader 5AR inhibition profile together with good tolerability and safety record make dutasteride an excellent candidate for reducing drinking in humans given the effects of finasteride in reducing alcohol self-administration in mice (Ford et al. 2005). The sequential actions of 5AR and the *AKR1C3* gene product 3α-HSD, which are the focus of this study, are illustrated in Figure 1 for the metabolism of testosterone to DHT and to the neuroactive steroid 5α-androstan-3α,17β-diol (aka 3α,5α-androstanediol).

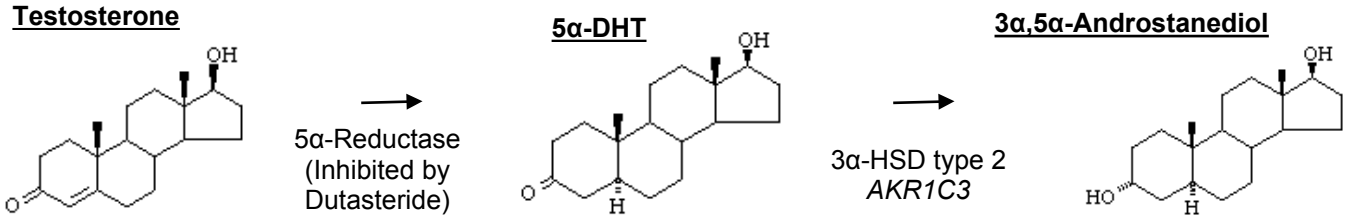

Figure 1. Biosynthesis of DHT and the neuroactive steroid 3α,5α-androstanediol from testosterone. Dutasteride blocks 5AR, the first enzyme in this pathway. The *AKR1C3* gene product 3α-HSD type 2 reduces DHT to 3α,5α-androstanediol . A common polymorphism in *AKR1C3* is associated with AD (C.2.b). 3α,5α-androstanediol is metabolized to the water soluble elimination product 5α-androstan-3α,17β-diol,17-glucuronide (3α-diolG) which will be assayed to measure 5AR inhibition by dutasteride. 3α,5α-androstanediol can also be produced by the 17β reduction (also catalyzed by the *AKR1C3* gene product) of 3α,5α-androsterone. As illustrated for 3α,5α-androstanediol, 5AR and 3α-HSD are sequentially required for the generation of 3α,5α-androsterone from the precursor androstenedione.

Relevance of this proposal to the Alcohol Research Center at the University of Connecticut School of Medicine. This project is an extension of prior research on the pharmacotherapy of alcohol dependence (AD) and heavy drinking that has been conducted at the UConn ARC for the past 20 years including clinical trials of fluvoxamine, fluoxetine, nefazadone, naltrexone, zonisamide and topiramate. This project will focus on reduction of drinking in heavy drinkers by a novel pharmacologic approach, manipulation of neuroactive steroid production. Recruitment for this study will benefit from implementation at all UConn clinical sites beginning in mid-2012 of Screening, Brief Intervention, and Referral for Treatment (SBIRT) for alcohol use problems for which Dr. Babor of the UConn ARC has been one of the innovators (Babor et al. 2007). Dissemination and training in use of SBIRT is the focus of Dr. Babor's component of the UConn ARC P60 renewal application. Identification of genetic associations with AD and alcohol use risk factors has been a focus of research for UConn ARC investigators during the past decade. The current study is in part motivated by recent ARC supported research which identified common polymorphisms in neuroactive steroid biosynthetic enzyme genes

as being associated with AD (section C.2.b.). Finally, this project employs daily monitoring technologies refined by ARC investigators in prior treatment trials. The study benefits from the involvement of ARC investigators with complementary backgrounds, Dr. Covault (psychiatrist with experience in prior ARC pharmacologic treatment trails of AD and in human genetic studies), Dr. Tennen (psychological determinants of problem drinking and daily process investigations), Dr. Oncken (internist and smoking cessation clinical research expert who has been a collaborator on prior ARC pharmacologic treatment studies) and Dr. Feinn (biostatistician with prior experience in clinical trial data analysis).

C. Research Approach

C.1. Preliminary Studies.

C.1.a. Effects of dutasteride on drinking in a naturalistic setting (Covault et al., 2012).

In a recently completed study funded by an R01 to Dr. Covault, we used dutasteride to block de novo production of 5α-reduced neuroactive steroids to examine the potential role of neuroactive steroids on the acute effects of alcohol in male social drinkers. In a secondary analysis as part of this study we examined the naturalistic use of alcohol by subjects between monthly laboratory sessions as a function of dutasteride vs. placebo drug. In this study, subjects participated in 4 laboratory sessions at one-month intervals in which pre-treatment with dutasteride (4 mg) or placebo was paired 2-4 days later with a moderate dose of alcohol (0.8 gr/kg) or placebo alcohol in a laboratory setting. Two groups of males aged 21-45 were recruited: low intensity drinkers with at most 1 episode of heavy drinking (≥ 5 SDs) per month and moderate drinkers with ≥ 3 episodes of heavy drinking per month. The pharmacologic effect of dutasteride was measured by assay of serum 5α-androstan-3α,17β-diol,17-glucuronide (aka 3α-androstanediol glucuronide or 3α-diolG) as a biochemical measure of 5AR inhibition. 3α-diolG is the primary metabolic excretion product of 3α,5α-androstane neuroactive steroids, that has been shown to decrease in parallel with DHT following finasteride treatment in men (Rittmaster et al. 1989; Gormley et al. 1990). A single 4 mg loading dose of dutasteride produced a 70% (S.D.=14%) reduction in 3α-diolG levels as well as similar reductions in plasma levels of the neuroactive steroids allopregnanolone and 3α,5α-androstanediol measured by GC/MS. Dutasteride was well tolerated in combination with a moderate dose of alcohol and compared to placebo, reduced self reported sedative effects of alcohol. Other subjective effects were minimally impacted by dutasteride pre-treatment.

We additionally collected data on alcohol use between laboratory sessions both as a measure of study safety (i.e., to ensure that participation did not lead to increased hazardous drinking) and to examine whether exposure to single doses of dutasteride influenced drinking in the 3 weeks following each alcohol lab session. As illustrated in Figure 2, among 29 moderate drinkers (mean standard drinks/week=14) we observed a significant reduction in the number of heavy drinking days (HDD) during the first and second week following dutasteride exposures and in the total number of drinks per week in the first week after dutasteride but not placebo dosing. These results suggest that blocking neuroactive steroid production in moderate drinkers reduces reinforcing aspects of alcohol in a time-limited fashion following a single 4 mg dose of dutasteride resulting in reduced levels of drinking (Cohen's d=0.36 for HDD/wk1 and d=0.37 for SDs/wk1). No significant effect was seen for low-intensity drinkers (n=33), perhaps because of a floor effect for this group (baseline mean SDs/wk = 4). These results parallel pre-clinical studies reporting a reduction in alcohol self-administration in mice following 5AR inhibition with finasteride (Ford et al. 2005; Ramaker et al. 2011) and strongly support the rationale for the proposed clinical trial of dutasteride to reduce drinking in heavy drinkers.

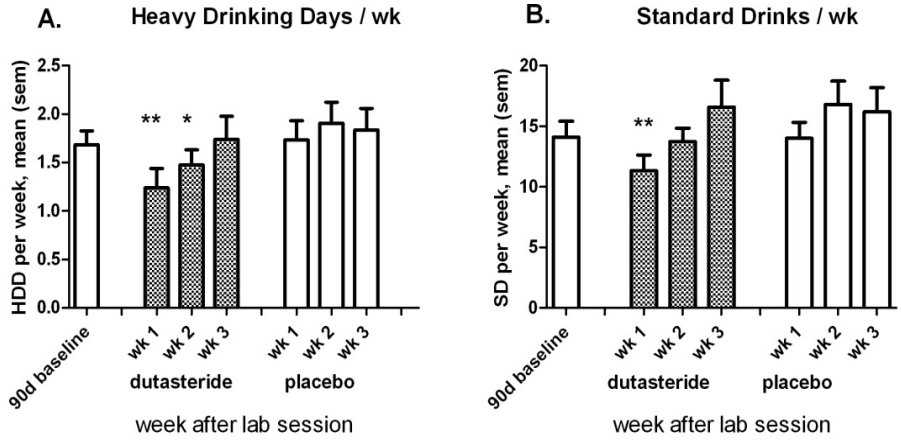

Figure 2. Weekly TLFB data following laboratory sessions with dutasteride (n=42) or placebo (n=42) pretreatment for 29 moderate-intensity male drinkers. Paired t-test statistics for post-lab drinking compared with 90-day TLFB baseline data. **A**. HDD/wk - significant decreases observed for weeks 1 and 2 following dutasteride lab, ** t= -4.15, p<0.001; * t= -2.29, p=0.028. **B.** SD/wk significant decrease for week 1 following dutasteride lab,** t= -3.12, p=0.003.

C.1.b. Polymorphisms in neurosteroid biosynthetic enzymes are associated with AD (Milivojevic et al. 2011). We used a case-control sample (1,083 non-Hispanic Caucasians including 552 controls and 531 subjects with AD) to test the association with AD of single nucleotide polymorphisms (SNPs) in genes encoding two enzymes required for the generation of endogenous neuroactive steroids: 5α–reductase, type I (*SRD5A1*) and 3α-hydroxysteroid dehydrogenase (3α-HSD), type 2 (*AKR1C3*), both of which are expressed in human brain. We focused on markers previously associated with a biological phenotype (Ellis et al. 2005; Figueroa et al. 2008). For 5AR, we examined the synonymous *SRD5A1* exon 1 SNP rs248793 and for 3α-HSD the non-synonymous *AKR1C3* SNP rs12529 (H5Q). The minor allele for both SNPs was more common among controls than subjects with AD: *SRD5A1* rs248793 C-allele (0.47 vs. 0.41**;** $\chi^2(1)=7.6$, p=0.006) and *AKR1C3* rs12529 G-allele (0.45 vs. 0.37**;** $\chi^2(1)=14.6$, p=0.0001). Evidence of an association with AD of polymorphisms in genes encoding neuroactive steroid biosynthetic enzymes, provides indirect evidence that neuroactive steroids are involved in biological effects of alcohol in humans.

Additional unpublished findings indicate that the *AKR1C3* AD risk allele is associated with increased frequency of heavy drinking in young men. In a sample of 532 male college students enrolled in a current UConn ARC study utilizing daily self reports of drinking, AD risk C-allele homozygous subjects (n=145) reported heavy drinking on 16% of days vs. 11% of days for protective G-allele homozygotes (n=120) with heterozygotes (n=267) reporting an intermediate frequency of HDD (ANOVA F=4.5; p=0.01).

C.1.c. Pilot feasibility study examining potential use of dutasteride in heavy drinkers.
Using pilot funds from the UConn ARC we are conducting an 8-week pilot study in men comparing dutasteride (4 mg loading dose followed by 1 mg daily) or placebo to examine the tolerability of dutasteride in heavy drinkers and the pharmacologic effect of this dutasteride dosing schedule on levels of the 5α-reduced neuroactive steroid metabolite 3α-diolG. The study is an approved project of IND 74,222 issued to Dr. Covault for the study of dutasteride in the setting of alcohol use. This IRB approved pilot study is being conducted in the UCHC Clinical Research Center outpatient clinic.
Subjects: 39 subjects were randomized to study medication or placebo, 36 have completed 8 weeks of medication. Participants enrolled in the study averaged 52.7 ± 8.9 (s.d.) years of age, 82% of whom met criteria for AD and consumed on average of 46±20 (s.d.) SDs / week with 5.1±1.9 (s.d.) HDD / week at study entry. 50% of subjects had a family history of alcohol dependence and 73% identified a goal of reducing drinking while 27% identified a goal to stop drinking.
Safety: Study medication has been well tolerated with similar rates of side effect reports for dutasteride vs. placebo during the 8-week medication treatment phase [mean number of side effects reported / subject: dutasteride=6.0±5.8 (s.d.) vs. placebo=8.4±10.8 (s.d.)]. The number of subjects reporting a sexual related side effect was also been similar between the two arms (n=3 for dutasteride and n=4 for placebo). Three subjects dropped out of treatment during the 8-week active phase (2 placebo, 1 active drug) and none due to medication side effects. Participation in completing daily self-reports was high [90%±10 (s.d.) of possible reports].
Laboratory measure of drug effect for the first 15 subjects showed a significant reduction in serum 3α-diolG for subjects randomized to dutasteride (n=9) at both 4-weeks (84% reduction; p=0.003) and 8-weeks (86% reduction; p=0.002) demonstrating effective inhibition of 5AR activity with the dutasteride dosing schedule proposed. There was no effect of dutasteride on serum testosterone levels at either 4- or 8-weeks (p=0.42 and 0.15 respectively) in this sample of heavy drinkers which mirrors the lack of effect of dutasteride on serum testosterone in other samples (Clark et al. 2004). There was no signficant change in serum 3α-diolG or testosterone in subjects in the placebo group (n=6).
Drinking outcomes: For 27 subjects completing the 8 week active phase as of July 1 (excluding 7 subjects with abstinence from outset (3 dutasteride and 4 placebo subjects) mixed model analysis showed a main effect of baseline drinking (p=0.005), study week (p=0.001), AKR1C3*2 genotype (p=0.029) and a trend for genotype by drug interaction (p=0.56) such that subjects gradually reduced drinking during the 8 weeks with AD risk allele homozygotes showing the highest level of drinking and the greatest benefit from dutasteride compared with placebo condition. For the 19 subjects who have reaced the 2 month post-treatment follow-up there was a significant drug x time interaction with a 48% decrease in SDs/w for dutasteride and a 39% decrease for placebo compared with baseline drinking [mixed model F(124)=4.68, p=0.032; effect size d=0.30].
Summary. These pilot study results support our ability to recruit and enroll subjects for the proposed study and indicate that dutasteride is well tolerated in alcoholic subjects with no effect of dutasteride on serum testosterone levels in the face of an 85% reduction in the 5AR enzyme metabolite 3α-diolG. Preliminary

drinking outcomes indicate that participants reduced drinking during the study period and that dutasteride may have greatest benefit for AKR1C3*2 alcohol dependence risk C-allele homozygotes.

C.2. RESEARCH DESIGN AND METHODS

General Design: This study employs a parallel-groups design in which dutasteride is compared with placebo to evaluate its safety and efficacy in reducing the likelihood of drinking and of heavy drinking by problem drinkers. The study will be conducted in the UCHC Department of Psychiatry Clinical Research & Evaluation Unit (CREU) and the Clinical Research Center (CRC). Random assignment to treatment group and double-blind conditions will be maintained throughout the study. The study will be conducted in three consecutive phases: a 1 to 2 week pre-treatment assessment period, a 12-week treatment period, and a 6-month post-treatment follow-up period. Patients will be provided medical management including brief counseling (adapted from Pettinati et al. 2004) at each treatment visit. Daily reports will limit retrospection bias during the treatment period. Objective laboratory data (serum GGT and %dCDT) will be used to further corroborate patient reports. Data obtained during the post-treatment follow-up period will make it possible to evaluate the durability of treatment effects beyond the period of active treatment.

Patients: Male drinkers who want to reduce or stop drinking will be recruited using advertisements in local media (including text ads in newspapers and weekly community circulars, radio ads on local radio stations, web ads on internet sites and web postings on community message boards), by posting/distributing recruitment materials at area Colleges and Universities, and in community settings with public posting areas (such as hospitals, town halls, public libraries, YMCA, health fairs/organizations), and by referral from UCHC medical clinics where screening for alcohol use problems using the NIAA Screening, Brief Intervention, and Referral for Treatment (SBIRT) protocol http://pubs.niaaa.nih.gov/publications/Practitioner/pocketguide/pocket_guide.htm is anticipated to be implemented at all UCHC clinics beginning in 2013. We anticipate that minority patients will be represented in proportion to the general population in central Connecticut. Approximately 200 men will be enrolled with the goal of randomizing 176 to medication and that at least 160 will complete 12 weeks of treatment. Based upon our success in recruitment for a pilot study of dutasteride (C.1.c) as well as other prior ARC clinical trials involving heavy drinkers, we are confident of our ability to achieve our recruitment goal. The introduction of SBIRT at all UCHC clinical sites will provide additional assurance of our ability to accomplish our study enrollment goal. Dutasteride is not recommended for use in women due to a potential birth defect in male offspring if a woman were to become pregnant while taking the medication. We will not enroll women in the current study as the risk of giving women dutasteride for treatment of alcohol use disorders is not justified until a potential benefit in reducing heavy drinking in male subjects has been shown.

C.2.a. Temporal Sequence of Screening: Prospective participants will first undergo phone screening to assess basic inclusion / exclusion criteria. Patients who appear to be eligible will be invited for an in-person screening. After informed consent is obtained, trained study staff will obtain a brief medical history and urine and blood specimens for clinical screening as well as for genotyping the *AKR1C3* H5Q polymorphism to allow balanced genotype distributions in the dutasteride and placebo treatment arms. At a subsequent baseline visit the patient will receive a physical and psychiatric examination by a study physician.

D.2.b. Criteria for Study Participation: Patients for this study are anticipated to have moderate levels of alcohol use disorder symptoms (typically meeting criteria for a diagnosis of alcohol abuse or mild to moderate AD) and want to reduce or stop their drinking. They will be asked to affirm a treatment goal of no heavy drinking days (≥5 standard drinks in a day).

C.2.b.1. Inclusion Criteria: a) male age 18 to 70 years, inclusive; b) have an average weekly ethanol consumption of ≥24 standard drinks [i.e., substantially in excess of non-hazardous drinking levels (Sanchez-Craig et al. 1995)]; c) be able to read English at the 8th grade or higher level and show no evidence of significant cognitive impairment; and d) be willing to provide signed, informed consent to participate in the study (including a willingness to stop or reduce drinking to non-hazardous levels);

For subjects who identify wanting to reduce drinking we will recommend they set a goal to of drinking not more than 4 SDs /day and not more than 14 SDs / week in keeping with NIAA guidelines for non-hazardous drinking. These recommended weekly limits for alcohol use represent a >40% reduction from the minimum limits of inclusion and a 70% reduction for the average subject in our pilot study (section C.1.c).

C.2.b.2. Exclusion Criteria: Although we will not set a specific upper limit in terms of drinks per week, we will exclude subjects with either a) no history of the capacity to reduce drinking from very high levels; b) a history of significant alcohol withdrawal symptoms (e.g. substantial tremor, autonomic changes, perceptual distortions, seizures, delirium, or hallucinations or of prior inpatient treatment of alcohol withdrawal); c) a current DSM-IV diagnosis of AD who on clinical examination by a physician, are deemed to be too severely alcohol dependent to permit them to participate in a placebo-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). Additional exclusion criteria include: d) a 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 elevations of >150% of the upper limit of normal or transaminase elevations >300% of the upper limit of normal (we will not exclude patients with hypertension, diabetes mellitus, asthma or other common medical conditions, if these are adequately controlled and the patient has an ongoing relationship with a primary care provider); e) have a serious psychiatric illness on the basis of history or psychiatric examination (i.e., schizophrenia, bipolar disorder, severe or psychotic major depression, organic mental disorder, current clinically significant eating disorder, or substantial suicide or violence risk); f) have a current DSM-IV diagnosis of drug dependence (other than nicotine dependence); g) are currently taking psychotropics other than medication for mood and/or anxiety disorder (with stable dose for at least 4 weeks), medications for treatment of Attention Deficit/Hyperactivity Disorder (with stable dose for at least 4 weeks), suboxone maintenance therapy for opioid use disorder (with stable dose for at least 4 weeks), or a non-benzodiazapine sleep medication or a low dose of benzodiazepine equivalent to 2 mg clonazepam or lorazepam per day; or h) are considered by the investigators to be an unsuitable candidate for receipt of an investigational drug.

C3. Study Drugs:
C.3.a. Dutasteride will be purchased commercially and formulated in opaque capsules by the Research Pharmacy Service of John Dempsey Hospital. Placebo will be formulated to match the active medication. Subjects will receive 4 mg of dutasteride or matching placebo capsules during first treatment visit (baseline study visit 2) followed by 1 mg daily for 12 weeks.
C.3.a.1. Pharmacodynamics: Dutasteride, a synthetic 4-azasteroid compound, is a competitive and specific inhibitor of both type I and type II steroid 5α-reductase with which it forms a stable enzyme complex with extremely slow dissociation. At clinical doses, larger reductions in DHT concentrations were observed with dutasteride than with finasteride, due to the limited inhibition of human type I 5AR by finasteride (Gisleskog et al. 1998; Gisleskog et al. 1999). In humans, type I 5AR is present in the brain, liver, adrenal gland and skin and is responsible for approximately one-third of circulating DHT. Type II 5AR is also present in the liver, is the predominant form in the 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 et al. 2001) where local generation of neuroactive steroids is thought to occur in addition to peripherally generated neuroactive steroids in the liver and adrenal gland.
C.3.a.2. Pharmacokinetics: Dutasteride has complex elimination kinetics (Gisleskog et al. 1999). Single doses of 0.5-5 mg are metabolized with a 3-4 day half-life, while drug accumulation following repeated doses produces delayed elimination with a half-life of weeks due to saturation of the rapid elimination pathway. The recommended daily dose for the treatment of benign prostatic hypertrophy in elderly men is 0.5 mg. The planned 4 mg loading dose, which was used as a single dose in our study of dutasteride paired with acute alcohol (C.1.a), and as a loading dose prior to 1 mg daily in a pilot study (C.1.c) is expected to produce an initial Cmax of 13-28 ng/ml [GlaxoSmithKline Phase I pharmacokinetic studies ARIA 1001 and (Gisleskog et al. 1998)], which is similar to the dutasteride blood level after 0.5 mg daily for 4 weeks (22 ng/ml, GSK Phase I pharmacokinetic studies ARIA 1003). This modest loading dose together with a daily dose of 1 mg dutasteride is expected to achieve a >90% inhibition of peripheral type II 5AR within 3 days and a 60% reduction in type 1 5AR by 4 weeks for a total reduction of DHT of $\cong$ 85% by 4 weeks (Gisleskog et al. 1998). Following discontinuation of study medication after 12-weeks, pharmacokinetic modeling suggests type I 5AR levels will return to normal $\approx$ 4-8 weeks later with a more prolonged recovery of type II 5AR (Gisleskog et al. 1998).
C.3.a.3. Dutasteride Adverse Effects Profile: Based on extensive clinical studies in men, dutasteride is well tolerated (Avodart, Prescribing information 2006, GlaxoSmithKline). In a series of three 2-year long treatment trials including 4,300 men aged 47-94 years (mean = 66 years), 0.5 mg of dutasteride daily for treatment of prostatic hypertrophy resulted in the following adverse effects compared with placebo: impotence (4.7% vs. 1.7%), decreased sex drive (3.0% vs. 1.4%), problems with ejaculation (1.4% vs. 0.5%), and development of

breast tissue (0.5% vs. 0.2%). In other clinical studies, daily doses of 5 mg (i.e., 5 times the daily dose in the current proposed study) were administered to 60 subjects for 6 months with no adverse effects beyond those seen at the more commonly used daily dose of 0.5 mg. In studies of normal volunteers, doses of up to 40 mg daily of dutasteride for 7 days have been administered without significant adverse effects. Dutasteride is not currently FDA approved for use in women due to the potential risk of a specific birth defect (reduced size of male external genitalia).

C.3.b. Placebo drug will consist of lactose powder formulated by the Research Pharmacy Service in gelatin capsules indistinguishable from the capsules containing dutasteride.

C.3.c. Medication Randomization and Drug Accountability: The UCHC Research Pharmacy staff will be responsible for medication randomization and dispensing. The Research Pharmacy will enter randomization variables (age, *AKR1C3* genotype, frequency of heavy drinking days for the 90-day period prior to screening, number of DSM-IV AD criteria, use of medication for treatment of co-morbid psychiatric condition, and drinks per drinking day from baseline 90-day TLFB) into an urn randomization program and provide to study staff a supply of study drug, as assigned. Although we will monitor capsule counts at each treatment visit, our primary measure of medication adherence will be daily IVR reports (section D.6.b.2). A daily diary method has been shown to yield results that are comparable to those obtained with electronic monitoring (r = .91) (Feinn et al. 2003).

C.4. Study Visits:

C.4.a. Visit 1 (Screening Visit): Prior to informed consent, subjects will have a breath alcohol (BrAC) measurement to validate sobriety. Following completion of informed consent, a brief medical and psychiatric history will be obtained by a study research assistant or nurse. Blood and urine samples will be taken for routine clinical laboratory evaluations, drug screening, DNA extraction and measurement of serum outcome measures GGT, %dCDT, the neuroactive steroid metabolite 3α-diolG and testosterone (to monitor for any unexpected negative effects of dutasteride on testosterone in heavy drinkers). Relevant portions of the Structured Clinical Interview for DSM-IV (SCID-I) will be administered by a research assistant to screen out subjects with major mental illness or dependence on other than alcohol or tobacco.

C.4.b. Visit 2 (Baseline Visit): 7-14 days after the screening visit, eligible subjects will return for a baseline visit where subjects will be trained to record their mood, desire to drink, self-efficacy and daily drinking using the IVR system and a physical examination will be performed by a study physician or APRN and any medication questions reviewed. Subjects will be instructed in use of study medication and given their initial 4 mg dutasteride or placebo dose and instructed to take two capsules (1 mg) daily at home for the remainder of the 12-week treatment period. Subjects will receive study medication for home use at the baseline and at each follow-up visit. At the baseline visit subjects will receive a one-week back-up supply of medication for use in case of lost capsule or need to reschedule bi-weekly follow-up visits. Subjects will be asked to bring unused medication to each follow-up visit for monitoring medication use. The UCHC research pharmacy will randomly assign subjects to dutaseride or placebo using an urn randomization to balance subjects on *AKR1C3* genotype, age and baseline alcohol use. Medication will be delivered or picked up from UConn Health IDS pharmacy for distribution to patients during IDS office hours (M-F 7:30am-4pm). For IDS off-hour appointments, medication may be obtained from IDS pharmacy and kept with study staff in a locked cabinet in a locked office in preparation for that appointment. In case a patient has a last minute cancellation or is a no-show, medication can be kept with study staff until the end of the business week. If the product is not distributed to the patient during that time, it will be returned to pharmacy.

C.4.c. Bi-weekly Clinic Visits 3 - 8: A brief Timeline Follow-Back Interview will be performed to track participants' daily alcohol consumption to augment IVR reports of alcohol use (see section D.9.a.2) and a trained research staff member will deliver the medical management intervention. Blood samples for study outcome measures (GGT, %dCDT, 3α-diolG, and testosterone) will be obtained at visits 5 and 8 (mid-point and end of treatment). We chose biweekly medication monitoring visits during the treatment period in order to optimize tolerability and thereby enhance treatment retention.

At the end of treatment week 12 (visit 8), subjects will complete a packet of questionnaires and be interviewed by research staff concerning their alcohol consumption and alcohol-related symptomatology (using the Alcohol section of the SCID-I, modified to ask about the past 30 days). Subjects will be compensated $50 for this end-of-treatment visit. Subjects requesting additional treatment for alcohol problems will be referred to local treatment centers. For subjects who withdraw early and do not wish to continue with study visits/procedures, all end-of-treatment procedures will be administered at the time of withdrawal. Such subjects will also be invited to participate in-person or by telephone to provide Timeline Followback data at 2, 4, and 6-months post-treatment.

C.4.d. Visit 9, 10, and 11 (Post-treatment Assessment Visits): To evaluate the durability of treatment effects, patients will return to the clinic for post-treatment assessments 2,4, and 6-months after completion (or for early terminators, scheduled completion) of treatment. We will attempt to reach all subjects directly or via their locator. At this visit, the subject will complete the self-report packet of questionnaires and will be interviewed by the research staff. Blood samples for measurement of serum GGT, %dCDT and 3α-diolG will be obtained. Subjects will be paid $50for the two and four month post treatment visit and $75 for the six month post-treatment assessment visits. Subjects will be eligible to request drug assignment information after their 6-month post-treatment assessment.

C.5. Medical Management: The physician will meet with the subject at the beginning of treatment and will consult at least weekly with the study staff to monitor potential study related side effects and adverse event occurrence. The physician will evaluate the subject should severe or persistent adverse effects occur. At each treatment visit (2-7) subjects will receive brief counseling as part of medical management, which is described in detail below.

C.5.a. Medical Management (MM) [Adapted from (Pettinati et al. 2004)]: The base manual for this intervention was developed for use in the Combine Study (Anton et al. 2006) to provide a basic form of clinical intervention supporting effective pharmacotherapy, to be used in conjunction with prescribed medication, and to be easily implemented by medically trained practitioners in non-specialty settings. A modified MM protocol that includes 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 treatment will also support subjects' efforts to reduce their drinking, with the study staff making direct recommendations, in keeping with each participant's treatment goal, for stopping alcohol use or reducing drinking.

The first MM session (study visit 2; 30-40 minutes) will consist of a review of the results of the initial evaluation, identifying any medical concerns related to drinking and reinforce subjects' treatment goal of stopping or reducing drinking to non-hazardous levels. This session will also use the self-help brochure "Cutting Back – A sensible approach to drinking and health" developed at the UConn ARC (Babor et al. 2006) to encourage drinkers to self-evaluate their drinking and set goals to stop or reduce drinking. It provides lists of negative health consequences of drinking, situations under which alcohol should not be used, benefits of cutting back, common triggers / reasons for drinking too much and a personal drinking contract to complete with choice of abstinence or to cut back to non-hazardous levels. This bibliotherapy brochure will encourage subjects to develop their own personalized motivational list for supporting their treatment goal. The subject is then provided with a rationale and information about pharmacotherapy. The study staff will use the subject's history of taking medication to establish an individualized plan to promote medication adherence. The session is completed by answering any questions or concerns that the subject has about treatment.

Subsequent MM treatment sessions (15-20 minutes) will be conducted biweekly for the 12 weeks of active treatment. During these sessions, the study nurse will perform a review of the subject's general functioning, obtain vital signs, weight, BrAC 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). Men who wish to reduce rather than stop drinking will be advised to consume not more than 4 standard drinks per day and 14 standard drinks per week. Because subjects will not be physically dependent on alcohol, reduction of heavy drinking is a safe and ethical goal.

Subject's receipt of other professional, self-help, or other treatments will be monitored during the study. Subjects will not be withdrawn from the study if they receive treatment outside the study, which in our experience with this population is relatively rare. However, we will monitor its occurrence and if group differences are found, a measure of additional treatment received will be incorporated in the data analysis.

C.6. Assessments:

C.6.a. Laboratory/Medical Assessments: A physical examination, urinalysis, urine toxicology, CBC, and a chemistry panel (which includes electrolytes, liver enzymes [ASAT, ALAT, GGT], bilirubin, BUN, and creatinine) will be used to screen subjects for medical exclusion criteria. Serum will be archived for HPLC measurement of carbohydrate deficient disialotransferin (%dCDT; Clinical Neurobiology Laboratory, Medical Univ of S. Carolina) as a serum marker of heavy drinking. %dCDT is considered highly specific for heavy

drinking, and has been recommended as an alternative or to complement GGT measurement (Myrick et al. 2001). Serum 3α-diolG will be measured using a commercial ELISA kit as a biochemical measure of 5AR inhibition by dutasteride. Serum testosterone will be measured using an Immulite 1000 instrument in the CRC lab to monitor for any unexpected negative effects of dutasteride on testosterone in heavy drinkers. Additional blood samples will be obtained at midpoint, end of the 12-week treatment phase and at the two follow-up visits to assay GGT, %dCDT, 3α-diolG and testosterone. Weight, blood pressure and pulse will be obtained at each treatment visit. Additional research laboratory testing: A portion of the blood samples collected will be processed and stored for later analysis of biological correlates (including RNA) of dutasteride medication effects or of change in alcohol consumption.

C.6.b. Psychological/Behavioral Assessments: The assessments listed below were chosen because they: a) are standard, widely used assessments to maximize comparability of findings with prior treatment studies of alcohol dependence and problem drinking, b) measure multiple outcome criteria, since a reduction in drinking may or may not result in improvement in other domains, and c) assess for potential change in depression or anxiety related to treatment as additional safety measures.

C.6.b.1. Areas assessed only at Visit 1 (in person screening):

a. Sociodemographic patient information: Medical history, family history of alcoholism, marital status, educational and occupational information and substance abuse treatment history.

b. Locator information: Study staff will identify subject locators on the basis of relationship to client, duration and current status of relationship, frequency of contact with the subject, and willingness to participate. Locators are contacted when efforts to reach a subject are unsuccessful, which contributes both to maintaining subjects in treatment and data collection.

c. Psychiatric diagnosis: The Structured Clinical Interview for DSM-IV (SCID-I/P) (First et al. 1997) will be used to classify subjects according to the presence or absence of major psychiatric disorders including AD. This, together with the physician's unstructured psychiatric interview (visit 2), will be used to assess exclusion criteria for serious psychiatric disorders. The SCID-I/P will be administered at screening visit and the alcohol portion of the SCID will be administered at treatment end-point and the 2, 4, and 6-month follow-up visits to evaluate presence of current alcohol dependence criteria after treatment.

d. Family history of alcohol dependence: This interview systematically questions an informant about the presence of psychiatric illness in relatives. We will use the alcohol section of the Family History Assessment Module FHAM (Rice et al. 1995) the subject will be asked to provide information concerning his biological relatives history of alcohol use, however, names of family members will not be obtained.

Table 1: Schedule of Assessments

Study Visit	V 1 Screening	V 2 Baseline	Bi-weekly phone call	V 3-7	V 8 End-point	V 9: 2-mo follow-up	V 10: 4-mo follow-up	V 11: 6-mo follow-up
Time relative to Medication		Start medication	wks 1,3,5	wks 2, 4,6,8,10	Wk 12 End medication			
Medical History, SCID, Fam Hx, Clinical lab tests, blood for DNA	X							
Timeline Follow-Back Interview	X	X		X	X	X	X	X
Vital signs & weight	X	x		x	x			
Alcohol Effects Questionnaire	X				x		x	x
Study outcome blood samples	X			wk 6	X	X	X	x
Physical Exam & Clinician review of Medical History		X						
Penn Alcohol Craving Scale (PACS)		X		X	X	X	X	X
SIP, DMQ, BDI, STAI		X		wk 6	X	X	X	X

Daily IVR call		X	X	X	X			
Side Effect Checklist			X	X	X	X		
Medical Management		X		X				
MED-Q					X			
Follow-up Interview (Alcohol SCID)					X	X	X	X

C.6.b.2. Areas assessed daily during the active treatment period: IVR will be used to collect daily ratings of alcohol subjective effects, mood, common triggers for drinking, past day drinking and medication usage. To facilitate the daily IVR interview, each patient will be provided with a wallet-sized interview guide with key term(s) for each interview question in the order in which it is presented by the system. A follow-along sheet detailing each question in the IVR phone call, including answer options, will also be given to subjects during the training session as a guide, and to assist the subject with the first few IVR call sessions.

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 four categories of alcoholic beverages: beer, wine, liquor and "other." 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. The time of the calls (5-10 PM) was chosen to balance a variety of patients work schedules and to reduce the potential for patients to have engaged in heavy drinking prior to making the calls. Once a patient is taught to complete the telephone interview, the time required each day is typically less than 5 minutes.

b. *Stimulating and Sedative Effects of Alcohol*: As an assessment of whether dutasteride moderates the intoxicating effects of alcohol, four probes will be included to assess how “buzzed, stimulated, calming or drowsy” patients felt who drank alcohol on the night prior or day of IVR.

c. 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, one from each octant of the circumplex model of mood experience (Larsen and Diener 1992), with each adjective rated on a 5-point scale (0 = "not at all" to 4 = "extremely"). The octants measure unpleasant (*sad, angry*) and pleasant (*happy*) mood; high activated (*active*) and low activated (*tranquil*) mood; activated unpleasant (*nervous*) and activated pleasant (*enthusiastic*) mood; and unactivated unpleasant (*bored*) and unactivated pleasant (*relaxed)* mood.

d. 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 events on drinking.

e. Daily medication usage: Using IVR, subjects will report daily medication use. Additionally, at each bi-weekly study visit, subjects will be asked by the study staff to indicate the number of study drug capsules taken each day. This method has been shown to be highly correlated with electronic monitoring of medication adherence (Feinn et al. 2003).

C.6.b.3. Areas assessed biweekly during the active treatment period and follow up visits:

a. Alcohol use patterns: The 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 each of the two follow-up evaluations. This interview procedure will provide quantity/frequency of alcohol consumption data for each day during the period prior to the interview. We will also be collecting daily measures of alcohol consumption using IVR during the active treatment period because despite evidence of the reliability and validity of the TLFB when used by trained interviewers, the TLFB is less useful for detecting patterns of alcohol consumption that vary on a day-to-day basis (Carney et al. 1998; Searles et al. 2000). Daily IVR reports will also enable us to examine co-variation in daily mood and daily events with alcohol use in order to address whether dutasteride moderates associations between daily mood or daily events and drinking as our group has found using IVR methods for treatment with naltrexone (Kranzler et al. 2004; Armeli et al. 2006).

b. Alcohol Craving: 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 as week (Flannery et al., 1999). The PACS has been shown to predict subsequent drinking during alcohol treatment trials (Flannery et al., 1999, 2003).

c. Medication adverse effects: Subjects will provide reports of side effects at each bi-weekly phone visit and study visit during the active treatment phase and 2-month follow-up visit using a list of adverse medication

effects derived from prior studies of dutasteride (any ongoing potential medication side effects reported at the 2-month follow-up will be assessed again at 4- and 6-month follow-up visits as needed).

d. Measures of treatment received: Records of 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.

C.6.b.4. Areas assessed at intake, midpoint, end of treatment and at follow-up visits:

a. Alcohol-related problems: The Short Inventory of Problems (SIP). The SIP is a 15-item instrument derived from the Drinker Inventory of Consequences (DrInC), which was developed for use in Project MATCH as a measure of alcohol-related consequences.

b. Psychological symptoms: a) The Beck Depression Inventory (BDI), a 21-item self-report measure of depressive symptoms, yields a total score that ranges from 0 to 63 (Beck et al. 1961). The BDI is generally regarded as a sensitive self-report measure of depressive symptoms, and will be used to explore the relation between depressive symptoms and treatment. b) The State version of the Spielberger State-Trait Anxiety Inventory (STAI), a 20-item self-report questionnaire (Spielberger 1983), will be used to provide concomitant monitoring of anxiety symptoms.

c. Drinking Motives: Drinking motives will be measured with the Drinking Motives Questionnaire [DMQ; (Cooper et al. 1992; Cooper 1994)] to explore potential changes as a result of treatment in drinking motives. This instrument contains 20 items with 4 subscales, drink to a) 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 midpoint, end of treatment and at the 2,4, and 6-month follow-up visits.

d. Alcohol outcome-expectancies will be assessed with 24 items from the Alcohol Effects Questionnaire [AEQ; (George 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 AEQ will be administered at baseline and for those subjects who continue to drink again at midpoint, end of treatment and at the 4 and 6-month follow-up visits.

e. *Integrity of the double blind:* A Medication Questionnaire (MED-Q) will be completed by the subject at the end of treatment (or at the time of treatment discontinuation for subjects who do not complete the 12-week 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 coming to that conclusion.

C.6.b.5. Methodological Problems in Daily Monitoring:

i. Daily Recording: A research assistant will monitor the IVR call generated dataset regularly to review whether subjects are supplying daily responses and if not that problems and questions are promptly addressed. Subjects who fail to call in during the allotted time receive a computerized reminder call [which has been shown to increase the response rate by nearly 10% (Kranzler et al. 2004)]. Monetary incentives will be used to encourage subjects to make calls daily. Subjects will be paid $1 for each telephone call completed and an additional $3 for each week in which they complete all calls, to a maximum of $120 ($10 per week for 12 weeks). Although this is less than is paid for daily reporting in other studies, we have found that subjects in treatment studies do not require the same level of incentives to promote adherence to daily reporting as is the case for studies in which no other benefits accrue to participation.

ii. Reactivity to Monitoring: Intensive self-monitoring using daily diary procedures has the potential to influence the behaviors being measured by increasing awareness of the temporal contingencies between behavior and internal or environmental triggers, or by initiating self-focused attention (Tennen and Affleck 1996). Measurement reactivity may be minimized through the use of diaries which, like the one to be used here, involve recording more than one behavior (Hayes and Cavior 1980) and limit recording to once a day (Tennen et al. 2000). Stone et al. (Stone et al. 2003) found little support for reactivity, defined as temporal shifts in the dependent variable (pain) or changes in pain recall, associated with daily monitoring.

iii. Validity of Reports: The ability of individuals to accurately record their behavior when they are intoxicated presents potential problems. Although there is no reason to expect that the effects of alcohol on validity of self-report would be greater in daily monitoring than for retrospective recall of intoxicated periods using the TLFB method, we chose to have patients make daily calls between 5 and 8 PM, to reduce the potential for patients to have begun drinking heavily prior to making the calls. Prior comparisons of IVR and

TLFB indicate subjects underreport drinking on TLFB vs. daily IVR reports (Tucker et al. 2007). In a UConn ARC study of targeted naltrexone, in which daily monitoring was used to measure daily events, mood, desire to drink, and drinking behavior, meaningful within-person associations were observed among these measures in the context of naltrexone treatment (Kranzler et al. 2004; Armeli et al. 2006).

C.7. Genotyping: Genotyping for urn randomization will be done using Cells-to-Ct assay reagent (Applied Biosystems, Inc) to allow rapid genotyping at the *AKR1C3* rs12529 SNP directly from blood. TaqMan allelic discrimination assays have been designed and used previously by our group for the rs12529 polymorphism in the *AKR1C3* gene that we indentified to be associated with alcohol dependence (Milivojevic et al. 2011) and with heavy drinking in college students (Milivojevic in preparation). The anticipated gentotype distribution frequency based on a sample of 531 AD subjects is GG 0.13; GC 0.49; CC 0.38. Reference DNA samples with each of the three possible genotypes at rs12529 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. Secondary analysis will examine whether polymorphisms in the genes (*SRD5A1* and *SRD5A2*) encoding the enzyme 5α-reductase type 1 and 2 which are the targets of dutasteride or other neuroactive steroid metabolic genes might also moderate treatment response. Polymorphisms in GABA(A) subunit genes will be considered as potential moderators of treatment outcome as neuroactive steroids act via GABA(A) receptors and we have previously reported that a polymorphism in *GABRA2* was associated with treatment response in the Project MATCH alcohol study (Bauer et al., 2007). Secondary analysis for Aim 4 will examine genetic variations in the genes *SLC6A4, NPY* and *FKBP5* that we have found to moderate stress related drinking among college students (Covault et al, 2007; and unpublished data). With continued 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.

C.8. Data Analysis:

C.8.a.1. Safety: Safety will be analyzed using categorical outcomes, defined by the type and severity of adverse effects. Summary measures of adverse events (AEs) will be developed by organ system from the adverse event checklist and will be compared for patients receiving dutasteride or placebo using χ^2 analysis. Comparisons will be conducted on 1) the number of patients in each of the two groups who report AEs, 2) the number of patients in each of the two groups who report moderate-to-severe AEs, and 3) the number of patients in each 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.

C.8.a.2. Efficacy: An important initial consideration will be to identify baseline differences between groups that may have occurred despite the use of urn randomization. The distribution of outcome data will also be examined prior to analysis, to determine the need for transformation and whether parametric analytic methods can be utilized. Successful outcome will be defined in terms of three primary dependent measures: SDs/week, HDDs/week, % of subjects with no HDDs, and % of subjects with non-hazardous drinking (no HDDs and SDs/week <15). Patients will be followed irrespective of whether they continue to receive treatment, so that analysis of both primary drinking measures and secondary outcomes will include all data available for the 12-week treatment period. Data for analyses of drinking outcomes during the 12-week treatment period will come from the daily IVR reports (missing IVR report days which will be coded as the larger of either 5 standard drinks (i.e. a HDD) or the IVR average daily use for the week reporting interval). Analysis of drinking for the 6-month follow-up period will be based on TLFB data collected at each follow-up visit. Secondary outcomes will include mean daily alcohol consumption, %dCDT levels (change relative to baseline), and severity of alcohol-related problems (as measured on the SIP and number of DSM-IV AD criteria).

Efficacy analyses will be performed using linear mixed models implemented in SPSS. Medication group will be treated as a factor and treatment week as a continuous covariate. An interaction term between medication group and week will be used to evaluate the efficacy of dutasteride compared to placebo in reducing drinking behavior over time. Pretreatment drinking will be controlled for using TLFB drinking data for the month prior to screening as a covariate. Treatment goal (stop vs. reduce drinking) will also be included as baseline covariate. The robustness of results will be evaluated by running the model under three different conditions: 1) all provided information, 2) only completers, and 3) imputation where missing days are coded as HDDs for subjects who fail to complete treatment.

For aim 3, analysis of drinking outcome variables will be repeated by including genotype at the *AKR1C3* rs12529 polymorphism as an additional between-subject factor.

C.8.a.3 Examination of daily measures.

Multilevel models will be used to examine the relations among daily measures of mood, daily event triggers and the frequency of drinking and of heavy drinking (level 1 measures) and their moderation by medication (level 2 measure). To examine how the within-person processes vary across individuals (i.e., cross-level medication interactions), the level 1 parameters are considered as outcomes in the level 2 model. Of specific interest is how the level 1 slopes (e.g., the associations between mood or daily event triggers and heavy drinking) vary as a function of experimental condition (dutasteride vs. placebo). Control variables (baseline heavy drinking, depression symptom score, baseline AD symptom severity) will also be included in level 2 predictive models. The utility of each level 2 predictor will be determined by the significance tests of the level 2 partial regression slopes.

C.8.b. Sample size considerations:

The proposed sample size of 176 randomized with goal of 160 completing 12-weeks of treatment with 80 per treatment group, is powered (80%) to show statistical significance (α=0.05) for medium effects d=0.45. The observed effect during the 1st week after dutasteride exposure in the naturalistic non-treatment study described in section C.1.a., was of this magnitude (d=0.37 for HDD/wk and SDs/wk outcome variables) while the pilot results from indicated a somewhat smaller effect size of d=0.3. For Aim 3 the proposed sample has 70% power to detect a d=0.6 effect size for genotype at α=0.05 contrasting AD risk C-allele homozygotes (freq=0.38) with protective G-allele carriers (freq=0.62).

C.9. 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 4/mo		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■			
6-month follow-ups					■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Data entry & cleaning			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Data analysis & Report writing													■	■	■	■	■	■	■	■

D. LITERATURE CITED

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E. PROTECTION OF HUMAN SUBJECTS

E.1. Patient population: Outpatient male problem drinkers identified through advertisements and referral from UCHC clinics will be randomized to study medication. We anticipate enrolling 200 subjects for screening visits in order to randomize 176 subjects to medication with a goal of 160 subjects completing 12 weeks of study medication. Patients must be heavy drinkers (aged 18-70) who are motivated to stop or reduce their drinking to safe levels. All patients will undergo careful medical and psychiatric assessment and must meet all inclusion and no exclusion criteria (as described in the Methods section above) to qualify for this study. The patients will all be adults in good physical health who are competent to provide consent.

E.2. Research material: 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.

E.3. Recruitment and 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 UCHC and affiliated primary care and dental clinics; advertisements in local media (including text ads in newspapers, magazines; radio ads; web ads and web postings on community message boards); posting/distributing recruitment materials at local colleges with public posting areas or other means of communicating with students and staff, such as electronic bulletin boards; through broadcast email messages at institutions (such as UCHC, 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 facilities throughout the Greater Hartford area, including outreach to the minority communities in the area, we anticipate that approximately 15% of patients enrolled in the study will be African-American and 10% will be Latino.

E.4. Potential risks: There are several classes of potential risk to patients enrolled in this study:
E.4.a. 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.
E.4.b. Counseling: Medical management brief counseling has been used safely with alcohol-dependent patients in the COMBINE Study. Psychological risks are minimal and not different from those of equivalent non-study treatments.
E.4.c. Medications: Dutasteride is not reinforcing and is therefore not a drug of abuse. There are few serious adverse effects associated with dutasteride use. 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 placebo: 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 placebo 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). Dutasteride is not currently FDA approved for use in women

due to the potential risk of a specific birth defect (reduced size of male external genitalia). While it is theoretically possible to expose a pregnant women to dutasteride via semen, exposure of pregnant non-human primates intravenously to16x the potential exposure to 5 ml of semen daily (assuming 100% absorption of dutasteride) was without adverse effect on the offspring (Avodart, Prescribing information 2006, GlaxoSmithKline). While no precautions are listed in the package insert regarding exposure of female partners to semen, we will advise participants to use medically acceptable contraceptives.

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 placebo 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 et al. 2010). The trials demonstrated an overall reduction in prostate cancer diagnosis with dutasteride compared with placebo treatment (20% vs. 25% with placebo) but an increased incidence of high-grade (Gleason score 8-10) prostate cancer (1% for dutasteride vs. 0.5% for placebo) 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 placebo). Long-term treatment with dutasteride may increase the risk for the development of high-grade prostate cancer. The 12-week short-term use of dutasteride in this study of alcohol use is not expected to alter participants' risk of prostate cancer.

E.4.d. Interaction of Medications and Alcohol: We have not observed any clinically significant additive CNS effects of dutasteride in combination with ethanol in our recently completed study of dutasteride paired with moderately intoxicating dose of alcohol in >70 male subjects (Covault et al. in preparation).
E.4.e. Blood and Urine Collection: These procedures are performed in large measure for baseline screening to safeguard patients. Additional bloods are drawn for research measures of alcohol 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.
E.4.f. Rating Scales and Questionnaires: These, including daily reports, are all 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.
E.4.g. 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. Given the small likelihood of breach of confidentiality (NB: in over 10 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.

E.5. Procedures to minimize potential risks: Inclusion criteria and the use of trained research staff in initial screening will minimize acceptance of patients with insignificant alcohol use into the study. Careful pre-treatment 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 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. 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, and containing the emergency numbers of the PI and study physicians for 24-hour consultation. 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 un-blind the data 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.

E.5.a. Confidentiality: To avoid breach of confidentiality, patients' names will appear only on a consent form, a telephone screening form 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 subjects unique study ID will be deleted to generate a de-identified dataset. Patient visits will be scheduled and no information about the patient will be provided to anyone (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.

E.5.b. 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 all FDA-approved medications widely available for treatment of AD.

E.6. Anticipated benefits to patients and society: Benefits to patients include careful evaluation of their medical and psychiatric status and alcohol use and potential reduction in their alcohol consumption, which may improve their health and well-being. 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 the genetic and other moderators of dutasteride response will enhance the clinical utility of dutasteride for alcohol use problems and the process of medications development for alcohol treatment.

E.7. Comparison of risks and anticipated benefits to patients and society: The risks associated with the counseling are minimal. Although the medication presents some risk, it has been shown to be safe when administered for benign prostatic hypertrophy for long periods of time (years). The potential risks of these treatments are minor compared to the risk incurred by individuals who continue to drink heavily. The risk/benefit ratio thus appears favorable to the proposed treatments.

E.8. 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 study, or one of the other study physicians, will be charged with the duty of determining the severity rating of adverse events. The study staff (P.I., co-investigators, clinical research coordinator) are responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified, graded for severity and assigned causality, reported to the required entities, and compiled for periodic review. After assigning causality, the P.I. will decide the course of action for the study participant. The P.I. will evaluate every 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. Serious adverse events that are related to the study interventions and unexpected will be reported to the UCHC IRB and the NIAAA project officer within 48 hours. An annual report summarizing all adverse events will be prepared and reported to the NIAAA project officer. 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

Adverse events during the treatment will be reported to the UCHC IRB, as well as to the NIAAA on an annual basis, with serious adverse events that are related to the study interventions and unexpected being reported within 48 hours. 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 UCHC or to other local health service providers. 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.

Women of Reproductive Age: As noted above women will not be included in this study as dutasteride is not FDA approved for use in women.

Data and Record Safety/Confidentiality: Records, filed in the IRB office, verify that all research project personnel have completed training in the protection of human research subjects in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, Clinical research coordinator, etc.) will keep all study medical records containing personal identifiers in locked cabinets in a secure location. All electronic data and files (e.g., database, spreadsheet, etc.) containing identifiable patient information shall be password protected. Any computer hosting such files shall have a BIOS password to prevent access by un-authorized users. Furthermore, for systems not running Windows 2000/XP, a password-protected screen saver will be installed and configured to activate ten minutes after the computer has been idle. If patient data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en-route to the recipient with strong encryption levels (≥ 128 bits for symmetric encryption (DES) and ≥ 1024 bits for asymmetric encryption (RSA).

All research data and blood specimens will be stored without direct identifiable information and links to personal information will be destroyed at the end of the patients participation in the study to generate a de-identified dataset. Blood will not be used for the purpose of establishing cell lines. Any hard copy records associated with the study will be kept in locked offices in the Clinical Research Center or the Alcohol Research Center. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms until transfer to the clinical or research laboratory

Blood will be collected for DNA analysis. The information derived from analysis of the patients' DNA will not be provided to the patient, since at the present time the existing preliminary genetic data for risk of alcohol dependence or in predicting response to dutasteride treatment do not provide a basis for genetic counseling. Should that situation change over the course of the treatment trial, procedures will be developed in conjunction with the UCHC IRB, to provide patients with relevant information on genotype and to counsel them in relation to that information. While the study is open, DNA samples will be coded with a number that provides an indirect link to the patient's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study the sample will be kept in storage indefinitely. However, the sample will forever be separated from all personal identifiers. These de-identified samples may be shared with other researchers and used in other projects. The lab procedures for sample storage include a passcode-protected locked room, and/or secure storage freezers.