Decreased Alcohol Consumption Among Former Male Users of Finasteride with Persistent Sexual Side Effects: A Preliminary Report

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Background: There is a robust literature in rodents, but not in humans, on the interaction between finasteride and alcohol, particularly as it relates to neurosteroids. Finasteride has been shown to reduce alcohol intake and suppress alcohol preference in male mice. This study examines the role of finasteride in alcohol consumption in humans with male pattern hair loss.

Methods: The subjects were 83 otherwise healthy men who developed persistent sexual side effects associated with finasteride, despite the cessation of this medication for at least 3 months. Information from standardized interviews was collected regarding medical histories, sexual function, and alcohol consumption before and after finasteride use.

Results: Of the 63 men who consumed at least 1 alcoholic beverage/wk prior to starting finasteride, 41 (65%) noted a decrease in their alcohol consumption after stopping finasteride. This reduction typically began before discontinuing finasteride. Twenty men (32%) reported no change in their alcohol consumption, and 2 men (3%) reported an increase in their alcohol consumption. For the 63 consumers of alcohol, the mean number (±SE) of alcoholic beverages/wk declined from 5.2 ± 0.7 before finasteride to 2.0 ± 0.3 after finasteride ($p < 0.0001$). A major study limitation is the lack of a comparison group.

Conclusions: In former male users of finasteride who developed persistent sexual side effects, 65% noticed a decline in their alcohol consumption as compared to baseline. This finding is consistent with finasteride's ability to modulate alcohol intake in rodents. Further research is needed on the central nervous system effects of finasteride in humans.

Key Words: Alcohol, Allopregnanolone, Finasteride, γ-Aminobutyric Acid Receptor, Neurosteroid.

FINASTERIDE IS A 5α reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, a more potent androgen associated with male pattern hair loss (MPHL) and benign prostatic hypertrophy. Randomized controlled trials of finasteride for treatment of these 2 conditions have demonstrated increased rates of sexual dysfunction including low libido and erectile dysfunction (Traish et al., 2011). More recently, a case series of 71 men has reported that a subset of men who take finasteride experiences persistent sexual side effects despite the discontinuation of the medication (Irwig and Kolukula, 2011). In addition to low libido and lack of satisfactory orgasm, many of these men have other central nervous system (CNS) side effects such as depression and suicidal ideation (Irwig, 2012). In 2012, the United States Food and Drug Administration changed the product labeling of finasteride (Propecia®; Merck, Sharp & Dohme Corp., Whitehouse Station, NJ) to include the persistent sexual side effects. Although the incidence of persistent sexual side effects associated with finasteride is unknown, finasteride is a very commonly prescribed medication to millions of men for both MPHL and benign prostatic hypertrophy.

In adult men, finasteride significantly lowers plasma levels of α-reduced neuroactive steroids (Duskova et al., 2009). In addition to the androgen pathway, 5α reductase inhibitors also block progesterone and glucocorticoid pathways which are important for the biosynthesis of neurosteroids. For example, finasteride blocks the conversion of progesterone to dihydroprogesterone which is then converted to allopregnanolone (ALLO). In both humans and rodents, ethanol (EtOH) consumption increases production of ALLO in the plasma and hippocampus (Barbaccia et al., 1999; Torres and Ortega, 2004). Pretreatment with finasteride attenuates this rise in ALLO levels in the cerebral cortex of rats (VanDoren et al., 2000). ALLO and EtOH both modulate the γ-aminobutyric acid type A ($GABA_A$) receptors to produce sedative and anxiolytic effects (Majewska et al., 1986). Given the ability of 5α reductase inhibitors to interfere with the

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Received for publication January 4, 2013; accepted March 25, 2013.

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DOI: 10.1111/acer.12177

endogenous production of neurosteroids, this study seeks to examine the effects of finasteride use on alcohol consumption in adult men.

SUBJECTS AND METHODS

Subjects

Subjects were recruited in 2010 and 2011 from the author's previous studies relating to persistent sexual side effects of finasteride (Irwig, 2012; Irwig and Kolukula, 2011). Participants for this study experienced sexual side effects which began while taking finasteride and which persisted for at least 3 months despite discontinuation of the medication. Subjects were taking the medication for treatment or prevention of MPHL, and all men started and completed finasteride use before age 40. Men were excluded from the study if they reported baseline sexual dysfunction, chronic medical conditions, current or past psychiatric conditions, a history of taking psychiatric medications, or baseline use of nontopical prescription medications other than a short course of antibiotics. All subjects provided written consent to this study which was approved by the institutional review board of George Washington University.

Design

Telephone or spoken Skype standardized interviews were conducted with all subjects as previously described (Irwig and Kolukula, 2011). Subjects were asked about demographic information, medical and psychiatric histories, medication use, sexual function, and weekly alcohol consumption. One alcoholic beverage was defined as 1 glass of wine, 1 can of beer, or 1 shot of hard liquor. Subjects were asked the question, "Before starting finasteride, how many alcoholic drinks would you consume during an average week?" The question was repeated for their current alcohol consumption at the time of the interview. A change in alcohol consumption was defined as a difference in the number of drinks per week which were expressed as integers. Sexual function was assessed with the Arizona Sexual Experience Scale (McGahuey et al., 2000). This validated instrument consists of 5 questions that measure core elements of sexual function: libido, arousal, erectile function, ability to reach orgasm, and orgasm satisfaction. Each domain was measured bimodally, with a 6-point Likert scale ranging from hyperfunction (1) to hypofunction (6). Sexual dysfunction was considered present if the total score was at least 19 or if any 1 item was at least 5 or if any 3 items were at least 4. The sensitivity and specificity of this instrument to identify sexual dysfunction were 82 and 90%, respectively (McGahuey et al., 2000).

Statistical Analysis

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC) using $\alpha = 0.05$ to declare a result as statistically significant. Paired Wilks' Lambda tests were used to test differences in alcohol consumption and sexual function before and after finasteride use.

RESULTS

The demographic characteristics, finasteride information, and alcohol consumption data are presented in Table 1. The mean age of the subjects was 31.1 years (range 21 to 46), and the mean age for beginning finasteride was 25.8 years. The mean length of finasteride use was 26 months. The mean (±SE) total scores on the Arizona Sexual Experience Scale were 7.1 ± 0.2 before finasteride and 22.0 ± 0.3 after finasteride at the time of the interview (p-value < 0.0001).

Table 1. Subject Characteristics, Finasteride Information, and Alcohol Consumption

Demographic characteristics, $n = 83$	
Mean age (years, range 21 to 46)	31.1 ± 0.6
Ethnicity	
White	70 (84)
Asian	8 (10)
Other	5 (6)
Location	
United States	41 (49)
International	42 (51)
Sexual orientation	
Straight	78 (94)
Gay	5 (6)
Finasteride information	
Median age began (years)	25.8 ± 0.6
Length of use	
<1 month	9 (11)
1 to 3 months	13 (16)
3 to 6 months	8 (10)
6 to 12 months	14 (17)
1 to 5 years	25 (30)
Over 5 years	14 (17)
Duration of persistent sexual side effects after finasteride cessation	
3 to 6 months	6 (7)
7 to 11 months	7 (8)
1 to 2 years	31 (37)
3 to 5 years	24 (29)
6 or more years	15 (18)
Alcohol consumption after finasteride use, as compared to baseline, $n = 63$	
Decrease	41 (65)
No change	20 (32)
Increase	2 (3)

Mean ± SE are reported for mean age and mean age of beginning finasteride. The remaining data are n with percentages in parentheses.

Of the 83 subjects, 63 reporting drinking at least 1 alcoholic beverage/wk on average prior to starting finasteride. In this subgroup of 63 alcohol users, as compared to their baseline period before finasteride use, their alcohol consumption after finasteride was decreased in 65% of subjects, the same in 32% of subjects, and increased in 3% of subjects. Among these 63 men, their mean (±SE) weekly alcohol consumption was 5.2 ± 0.7 drinks before finasteride and 2.0 ± 0.3 drinks after finasteride (Wilks' λ F-value = 25.82, degrees of freedom 1/62, $p < 0.0001$). The largest reduction in alcohol consumption occurred among the 8 subjects consumed at least 10 drinks per week before finasteride usage. Although not formally assessed, some of the subjects anecdotally volunteered information that after finasteride, they no longer could tolerate alcohol the same as before. Specifically, alcohol increased anxiety, tiredness, and dizziness. Some subjects reported that intoxication occurred with fewer drinks than before, that they lost the sense of euphoria and relaxation previously associated with alcohol, and that they experienced longer times to recover from the effects of alcohol. Eighteen subjects reported giving up alcohol entirely.

DISCUSSION

In a group of otherwise healthy men who developed persistent sexual side effects associated with finasteride, alcohol consumption after finasteride discontinuation was decreased in 65% of subjects, the same in 32% of subjects, and increased in 3% of subjects. The mean weekly alcohol consumption per subject declined from 5.2 drinks before finasteride to 2.0 drinks after stopping finasteride. Many of the subjects expressed no longer being able to tolerate alcohol as before, and this led 18 subjects to completely stop drinking alcohol. The reduction in alcohol consumption typically began before the discontinuation of finasteride.

In male mice treated with finasteride for 7 days, there was a decrease in EtOH intake during the acute treatment and early withdrawal periods, in addition to suppressed alcohol preference (Ford et al., 2005a, 2008). These effects were dissipated with chronic finasteride treatment. However, finasteride-treated animals showed persistent attenuated levels of EtOH consumption for 2 weeks after treatment, despite a recovery in brain ALLO concentrations. In addition, exogenous ALLO acted in a dose- and time-dependent way to modulate EtOH intake (Ford et al., 2005b). Low doses of ALLO increased EtOH intake, whereas high doses of ALLO suppressed EtOH intake. ALLO initially increased EtOH intake but then decreased the number of licks over time. Similarly, a study of male rats found that different doses of systemically injected ALLO affected the self-administration of EtOH (Janak et al., 1998).

Within the brain, the hippocampus appears to be a critical structure in terms of alcohol and neurosteroids. In isolated rat hippocampal tissue, EtOH increases the local biosynthesis of ALLO. This, in turn, increases the amplitude and decay prolongation of $GABA_A$ receptor miniature or evoked inhibitory postsynaptic current amplitude (Sanna et al., 2004). Pretreatment with finasteride prevents this sequence of events. This study suggested that EtOH likely has a biphasic effect on the $GABA_A$ receptor. The immediate effect represents a direct interaction with the receptor. The delayed effect is likely mediated through neurosteroids such as ALLO. In another study with rat hippocampal tissue, lower concentrations of EtOH blocked long-term potentiation in the presence of ALLO (Izumi et al., 2007). Treatment of the slices with finasteride overcame the effects of high acute concentrations of EtOH. On a cellular level, EtOH increased the staining of ALLO in the CA1 pyramidal neurons of the rat hippocampus (Tokuda et al., 2011). This process was blocked by finasteride. This study found that EtOH's effects are due to activation of unblocked *N*-methyl-D-aspartate receptors.

Although most of the studies have focused on the hippocampus, another important region is the amygdala. Both the hippocampus and amygdala share important roles in both sexual function and motivational effects of alcohol (Pfaus, 2009). In the central amygdala nucleus of male rats, EtOH increased GABAergic transmission via pre- and postsynaptic sites (Roberto et al., 2003).

As opposed to the rodent literature, there are few human studies regarding alcohol, finasteride, and neurosteroids. In male adolescents, acute alcohol intoxication resulted in increased plasma levels of ALLO (Torres and Ortega, 2004). In a randomized controlled trial involving healthy male social drinkers homozygous for the A-allele variant of the GABRA2 gene which encodes the $GABA_A$ receptor α-2 subunit, pretreatment with high dose finasteride resulted in attenuated subjective responses to alcohol (Pierucci-Lagha et al., 2005).

Despite the current knowledge of the interaction between alcohol, finasteride, and neurosteroids, there are many remaining questions and avenues for further research. Neurosteroids have been found to be protective for neuronal health as it relates to apoptosis and formation of synaptic inputs (Charalampopoulos et al., 2004, 2008; Ge et al., 2008; Spritzer and Galea, 2007). In mice with Niemann Pick disease, a therapeutic injection of ALLO increased neuronal survival from 67 to 124 days and delayed neurological symptoms (Grobin et al., 2003). For the present study of men who continue to experience persistent effects for years after the discontinuation of finasteride, one might suspect that their brain architecture has been altered as a result of changes in neurosteroid levels. Because not all of the study subjects experienced decreased alcohol consumption, genetic variation likely underlies why certain individuals react in different ways to the same medication. In addition to the changes in alcohol consumption and responses to alcohol, many of the subjects volunteered other CNS symptoms including emotional flatness, depression, anxiety, decreased concentration, and memory loss. It has been shown that $GABA_A$ receptors have variable sensitivities to ALLO depending not only on alcohol but also on other factors such as stress, social isolation, and aging (Mellon, 2007).

Inherent limitations to this pharmacovigilance study include a lack of a comparison group, recall bias, and selection bias. Subjects had to retrospectively recall their average alcohol consumption before finasteride. The mean recall period for baseline alcohol use was 5.3 years. In terms of selection bias, the study population was limited to a small minority of men who developed persistent sexual side effects associated with finasteride. It is therefore unknown whether changes in alcohol consumption or sensitivity occur in general users of finasteride who do not report persistent sexual side effects. Consideration should be also given to potential confounders, particularly those related to psychopathology and age. Many of the subjects in this study suffered from depressive symptoms (Irwig, 2012) as assessed by the Beck Depression Inventory II, and some anecdotally reported that this led them to drink less as they participated in fewer social activities that involved alcohol. In addition, episodes of binge and heavy drinking have been shown to decline in the third decade of life, a time period that overlaps with the ages of many of the subjects in this study (Dawson et al., 2004;

O'Malley et al., 1988; U.S. Department of Health and Human Services, 2011). Although the modest effects of age on alcohol should be noted, they are unlikely to fully account for the magnitude of decreased alcohol consumption in this study, particularly as most participants noticed the decline during a relatively short-time frame of under 5 years, many under 3 years. Despite the recall bias and limitations mentioned, it is important to highlight that many of the men volunteered statements indicating that they could no longer tolerate alcohol as compared to before starting finasteride. The increased anxiety and other symptoms point to changes in the CNS that should be further explored.

CONCLUSIONS

Although finasteride is a widely prescribed medication for MPHL and benign prostatic hypertrophy, many clinicians are unaware of its effects on neurosteroids. In addition to reducing the concentrations of dihydrotestosterone, 5α reductase inhibitors also reduce the levels of ALLO, a neurosteroid linked to the major inhibitory neurotransmitter GABA. In this study of men who developed persistent sexual side effects associated with finasteride, nearly two-thirds noticed a decline in their alcohol consumption compared to baseline. This represents the first human study to describe changes in alcohol consumption associated with finasteride and is consistent with rodent studies. Further research is needed on the CNS effects of finasteride in adult men.

ACKNOWLEDGMENTS

I thank Richard Amdur, PhD for the statistical analysis and the study subjects for their time and participation.

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