Title of Study: Effects of Tolcapone on Decision Making and Alcohol Intake in Alcohol Users

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The Catechol-O-methyltransferase Inhibitor Tolcapone Modulates Alcohol Consumption and Impulsive Choice in Alcohol Use Disorder

NCT 02740582

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Study Protocol and Analysis

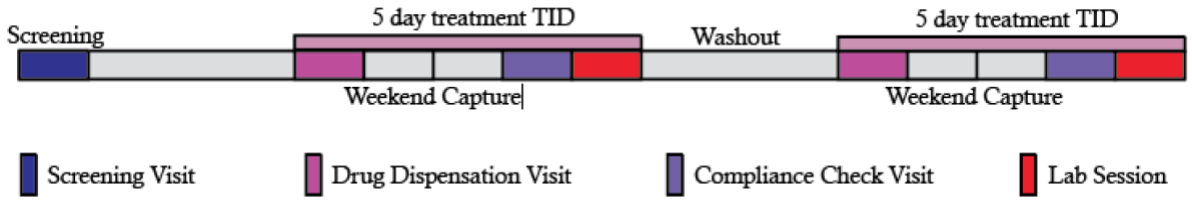
Experimental Design

Subjects participated in a total of seven visits: Screening, Drug Dispensation x 2, Compliance x 2, and Laboratory Session x 2 (described below). Upon completion of both the first randomized double blind drug cycle and a drug washout, subjects crossed over to complete the second drug cycle.

To increase subject retention, and given previous work that even a single dose of tolcapone can influence decision making (Kayser et al., 2012), we evaluated a 5-day treatment period. This 5-day dosing regimen included a weekend, thereby both allowing us to capture self-reported weekend drinking (Friday-Sunday) on study drug, and also permitting subjects to return on the final day of the treatment window for the Laboratory Session (on either a Monday or a Tuesday evening). Based on previous work with this subject population, we felt that subjects might display higher drinking over the weekends and therefore that we would be best able to capture a drug effect during this time.

The trial was registered at ClinicalTrials.gov, NCT 02740582.

Figure 1



Subjects

Non-treatment seeking individuals with AUD (ages 21 – 40; Table 1) were recruited via a Craigslist posting, which requested that subjects be "moderate to heavy alcohol drinkers", as well as referrals from study subjects. The age range was chosen to minimize safety concerns regarding possible tolcapone effects on hepatic function (Tan, Eastment, Poudel, & Hubbard, 2015) and to avoid age-related changes in the dopamine system that can begin as early as age 40 (Volkow et al., 1996). While there are important differences in treatment seeking and non-treatment seeking subjects (Rohn et al., 2017), we intentionally chose to evaluate the effects of tolcapone in a non-treatment seeking population to minimize both regression to the mean and the need to assess subject motivation. Using this population also represents an intrinsically more conservative approach, in that subjects who are not motivated to reduce alcohol consumption may be less likely to show large declines in alcohol consumption.

Following a brief telephone screening procedure, potentially eligible subjects were invited in for a screening visit.

Screening Visit

Written informed consent was obtained in accordance with the Institutional Review Board at the University of California, San Francisco. Study visits took place in the research clinic within the

Li Ka Shing building at UC Berkeley. Acute intoxication was assessed via a breath alcohol sensor (Alcomate, Palisades Park, NJ); subjects were required to have a 0.00 blood alcohol concentration (BAC) to provide consent. To capture multiple dimensions of alcohol use, inclusion criteria incorporated both self-reported alcohol consumption (>10 drinks/week for females and >14 drinks/week for males) and a requirement to meet DSM-5 criteria for AUD in the last 12-months (as assessed via the AUD section of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)). The mean AUDIT score in the study population was 14.3, and 98.1% of subjects showed an AUD severity of moderate or severe (Table 2).

Female subjects were administered a pregnancy test, and were required to be non-pregnant, non-lactating, and using a reliable contraceptive method. Exclusion criteria included a positive urine drug screen (with the exception of THC), or use of any illicit substance within 72 hours of the start of the study; current attempts to either reduce or eliminate alcohol consumption (e.g. via current enrollment in an alcohol or drug treatment program); history of alcohol related complications (e.g., liver failure/cirrhosis, pancreatitis, esophageal varices); abnormal results on tests of liver injury (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values greater than the upper limit of normal); regular use of any drugs with catecholaminergic actions such as SSRIs or amphetamines; and severely low or uncontrolled high blood pressure. Information about subjects' past substance use, psychiatric history, medical history, current medications, and family history of problem drinking was collected. The study clinician performed a physical examination, a 12-lead electrocardiogram, and a blood draw to evaluate markers of liver injury. To establish a baseline prior to laboratory bar sessions, subjects were also asked to perform components of a standard field sobriety test that assessed horizontal gaze nystagmus, walk-and-turn, and a timed one-leg stand. Together with evaluation of BAC, these direct measures of neurological function were used to ensure that subjects were free of alcohol-induced motor impairments prior to dismissal from the laboratory bar sessions. The screening visit concluded with the administration of behavioral inventories including the Alcohol Use Disorders Identification Test (AUDIT; (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993)) and the Barratt Impulsiveness Scale (BIS; (Patton, Stanford, & Barratt, 1995)). Eligible subjects were scheduled into groups of 4-8 subjects for study drug administration.

Study Drug

Study drug was provided by Valeant Pharmaceuticals. Wellspring Compounding Pharmacy (Berkeley, CA) held the study blind and re-compounded study drugs to add 10 mg riboflavin to both tolcapone and placebo in order to facilitate medication compliance checks: ultraviolet light was used to detect the presence of riboflavin in the urine at the Check Visit and the Laboratory Session. Enrolled subjects self-administered tolcapone (100 mg) or placebo three times a day (TID) for 5 days, for a total of 300 mg tolcapone per day. This dosing regimen is in keeping with the FDA approved dosing regimen for Parkinson's disease, the approved indication for tolcapone treatment.

Drug Administration Visit

Subjects returned to the clinic on a Thursday or Friday morning to begin the study drug administration cycle. Given that the half-life of tolcapone is 2.5 hours, we expect the drug reached steady-state at approximately 12.5 hours (5 half-lives). The initiation of drug administration on a Thursday or Friday was designed to capture weekend drinking (see below)

during the 5-day administration window. Subjects completed a side effects scale, a pulse and blood pressure check, and a pregnancy test (females). Subjects ingested their first dose of study drug under clinical supervision and were instructed to continue medication administration three times daily, ending on the 5th day (Monday or Tuesday) when they ingested their final dose at the start of the Laboratory Session (Figure 1). Subjects and investigators were blind to the medication condition. Medication bottles were equipped with Medication Event Monitoring System (MEMS) caps (AARDEX, Zurich, Switzerland) that generated a time stamp each time the bottle was opened. MEMS caps data were downloaded at each study visit.

Weekend Drinking
Subjects were instructed on "standard alcoholic drink" volumes and provided an information card for reporting weekend drinking. Subjects were contacted via a HIPAA compliant text message system each day during medication administration to capture the number of alcoholic drinks the subject had consumed the previous night. To confirm standard drink values, the type, amount, and volume of alcohol were reviewed in person with the study staff at the Compliance Check. "Weekend drinking" was calculated as the total number of alcoholic drinks from Friday to Sunday.

Compliance Check
Subjects returned to the clinic for a compliance check the day prior to their laboratory session. This visit assessed medication compliance (including evaluation of MEMS cap data), collected side effects information, and obtained a urine sample to confirm riboflavin florescence. All subjects had positive riboflavin screens at their study visits. MEMs caps data indicated that on at least 4 of the 5 treatment days, 95.5% of the subjects opened their MEMs cap 1x/day or more, 90.0% opened the MEMs cap 2x/day or more, and 59.1% opened the MEMs cap 3x/day or more, demonstrating reasonable medication compliance.

Laboratory Session
Subjects arrived at the clinic for the laboratory session (in groups of 4-8 subjects) on a Monday evening (for subjects started on a Thursday) or Tuesday evening (Friday start). Subjects were asked to fast for 1 hour prior to the start of the session and were drug screened and assessed for acute intoxication upon arrival. Those subjects with a positive screen or BAC were not permitted to consume alcohol. Subjects ingested the final dose of study medication immediately prior to completing the tasks below.

Delay Discounting Task
Detailed methods have been previously described and validated in a similar subject population (Boettiger et al., 2007; Mitchell et al., 2005). At the start of each trial, subjects were cued to one of four trial types: "Want", "Don't Want", "Sooner", and "Larger". For each of these trial types, subjects were presented with two hypothetical alternatives on the left and right sides of the screen: a smaller amount of money available sooner and a larger amount available at a future point in time. Subjects made a button press to select the option associated with the left and right sides of the screen in accordance with trial type. Subjects selected the option they wanted in the "Want" trials and the option they did not want in the "Don't Want" trials. "Sooner" and "Larger" trials, in which subjects simply identified the sooner and larger options respectively, were included as control conditions to ensure that subjects followed task instructions. The choice was

presented as one of six variations: a "sooner" option of "today" versus a "later" option of five future time points (1 week, 2 weeks, 1 month, 3 months, or 6 months), or a "sooner" option of "3 months" versus a "later" option of "6 months". The "larger" value consisted of six amounts ($1, $2, $5, $10, $20, or $100), while the "sooner" value represented one of four percentages (70%, 85%, 90%, and 95%) of the larger delayed amount. Subjects completed 6 blocks of 47 trials each (for a total of 282 trials) presented in pseudorandom order and were permitted to take breaks between each block. The "Want" condition comprised 50% of all trials, the "Don't Want" condition comprised 34%, and the two control conditions combined comprised 16% of the trials. The primary behavioral outcome was the impulsive choice ratio (ICR), which represents the ratio of the number of sooner choices to the number of total choices in the "Want" condition. More impulsive subjects are thus characterized by higher ICR values. Previous work has demonstrated that this intuitive score correlates strongly with other model-based measures of delay discounting (Kayser et al., 2012; Kayser, Mitchell, Weinstein, & Frank, 2015; Mitchell et al., 2005). Study participants completed this task together in the same testing room prior to the laboratory bar.

Assessment of Side Effects

Subjects completed a side effects scale reporting the extent to which they were experiencing 17 side effects (scored on a 0 – 3 scale, indicating "none", "slight", "moderate", and "severe" effects) at each study visit. Because tolcapone may be hepatotoxic, the side effects were selected, in consultation with the FDA, to monitor effects associated with compromised liver function. All subjects who reported a side effect as "moderate" or "severe" were immediately evaluated by the study clinician. Over the course of the study, 11 subjects reported a moderate or severe side effect; 4 of those subjects were taking tolcapone at the time (see Results).

Laboratory alcohol consumption

The laboratory session included a proof-of-principle, group laboratory bar protocol. All behavioral testing occurred prior to any alcohol consumption. This protocol was designed to create a more naturalistic setting for social drinkers. Laboratory sessions took place in a room outfitted with couches, coffee tables, and music to achieve a social bar-like atmosphere. Minimal guidance on social interaction was prescribed: subjects were seated together, instructed not to use phones during the experiment, and encouraged to interact during the laboratory session. To best account for variability in administration times across subjects, the final dose of study medication was ingested in the laboratory, and the laboratory session was timed to be in the peak effective window of this dose. Eighty-minutes following the final medication administration, subjects were given a priming drink. Alcohol content in the priming drink was calculated based on the subject's weight and sex and designed to bring the blood alcohol concentration (BAC) to approximately .04. The formula for calculating grams of pure alcohol was based on the Widmark formula (Posey & Mozayani, 2007): $g = kg * r * BAC * 10$, where r = .68 for males and .55 for females, and where BAC = .04. Subjects were required to consume the priming drink within 15 minutes. Both alcohol and soda were refrigerated and drinks were served without ice to maintain a 1:3 ratio.

Following the priming drink, BAC was assessed via a breath alcohol sensor (Alcomate, Palisades Park, NJ). Subjects received 4 (empty) cups to represent the maximum of 4 drinks they could order during the 1-hour session. Each drink was ½ the size of each subjects' initial priming drink and valued at $4. Subjects were told that they had a pre-paid tab valued at $16 and the value of

any drinks they did not consume would be added to their study payment. Salty snacks and water were available throughout the session.

After the 1 hour drinking session, subjects were provided with dinner. Subjects were required to have BAC ≤ 0.04 and to pass a Field Sobriety Test (see above) before they were eligible for dismissal. All participants were driven home via car service (either Lyft or Uber).

Crossover

After the laboratory session and following a washout window, subjects were crossed over to the alternate study drug. Given the 2.5-hour half-life of tolcapone (Jorga, 1998), a minimum of 3 days of washout ensured that, if tolcapone were administered during the first cycle, at least 24 half-lives had passed before the second cycle began. To control for day-of-the-week effects on behavior, the crossover cycle was scheduled to begin on the same day as the first cycle, resulting in either a 3-day or 10-day washout window based on scheduling availability. To control for social dynamics, lab bar group composition was maintained across medication cycle crossover whenever possible; however not all subjects completed the laboratory sessions (see Statistical Analysis below).

Genetic Analysis

Although our sample size was not powered to examine genotype, an exploratory analysis was conducted to ascertain whether the previously published relationship between COMT and decision-making might also be apparent in this study sample. DNA was extracted from saliva samples by the UCSF Genomics Core using Gentra Puregene reagents and protocols and quantified using the Pico Green method (Molecular Probes/Invitrogen). COMT genotyping was carried out by direct DNA sequencing of genomic DNA using fluorescent Sanger chemistry and analyzed using Mutation Surveyor from SoftGenetics LLC. Sequencing genotype accuracy was cross-validated with TaqMan (Applied Biosystems, Foster City, CA).

Statistical Analysis

Our sample size was calculated based on previous changes in alcohol consumption observed in a laboratory bar setting (Mitchell, Bergren, Chen, Rowbotham, & Fields, 2009). We calculated that, for a mean difference of .5 drinks per session and a standard deviation of 1.2 drinks, we would need a sample size of at least 48 subjects to achieve an alpha of .05 with a power of .80 for the pilot group laboratory bar protocol. Due to low enrollment and high drop-out rates in this subject population, we projected that we would need to enroll 80 subjects to achieve a final sample size of 48 subjects.

We enrolled a total of 62 enrolled subjects, and 55 subjects successfully completed the weekend drinking paradigm. Of the 7 subjects who did not complete the paradigm, 1 was excluded for non-adherence to the study protocol, 1 asked to withdraw, 1 experienced a drug dispensing error, 1 did not show for the scheduled visit, and 3 subjects had positive urine drug screens at the first lab bar visit and ended their participation. 50 of 55 subjects completed both lab bar sessions. The 5 who did not complete both lab bar sessions had positive urine drug screens and were excluded from drinking at these sessions. Three additional subjects were excluded from the DDT decision making task analysis for performing at less than 60% accuracy on control trials designed to assess task compliance (Mitchell et al., 2005), leaving 47 subjects for the DDT analysis.

The primary outcome measure of "weekend drinking" was defined as total number of alcoholic drinks consumed (Friday to Sunday) to capture drinking on study drug across dosing schedules. Secondary outcome measures included the change in impulsive choice ratio (ICR) on the DDT task following tolcapone, the number of alcoholic drinks consumed in the lab bar, and the impact of genotype on tolcapone effects. Data is reported as mean ± SEM unless otherwise noted.

Change in weekend drinking and ICR on tolcapone versus placebo were assessed using a within subjects paired t-test. Differences in DDT responses across genotypes were assessed using a one-way ANOVA. The relationship between tolcapone effects on weekend drinking and ICR was assessed with correlation analysis. All statistical tests were conducted using VassarStats and Microsoft Excel V15.23.2.