Psychopharmacology
https://doi.org/10.1007/s00213-020-05599-5

ORIGINAL INVESTIGATION

The catechol-O-methyltransferase inhibitor tolcapone modulates alcohol consumption and impulsive choice in alcohol use disorder

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Received: 14 April 2020 / Accepted: 23 June 2020

Abstract

Rationale Individuals suffering from alcohol use disorder (AUD) demonstrate difficulty with decision-making and impulsivity that may be associated with impaired frontal cortical function. Therapeutics that enhance frontal dopamine tone could decrease impulsivity and in turn reduce alcohol consumption in individuals with AUD.

Objectives To determine if the catechol-O-methyltransferase (COMT) inhibitor tolcapone can attenuate alcohol consumption in individuals with AUD and whether this attenuation correlates with tolcapone-induced changes in laboratory-based decision-making tasks.

Methods We used daily self-report and a novel group laboratory bar task to assess the effects of randomized double-blind crossover administration of tolcapone (100 mg TID for 5 days) on alcohol consumption and laboratory tasks assessing impulsivity in 55 non-treatment-seeking subjects with AUD.

Results Tolcapone significantly reduced self-reported alcohol consumption ($t(54) = 2.05$, $p = 0.045$). The effects of tolcapone on drinking significantly correlated with changes in impulsive decision-making, such that subjects with the greatest decrease in impulsive choice on tolcapone also reported the greatest decrease in alcohol consumption ($r(45) = 0.40$, $p = 0.0053$). We did not see effects of tolcapone on laboratory bar consumption. Adverse event (AE) reporting was low, with no significant difference in frequency or severity of AEs on tolcapone versus placebo.

Conclusions These data demonstrate that COMT inhibitors such as tolcapone may be useful therapeutics for AUD.

Trial registration ClinicalTrials.gov Identifier: NCT 02740582

Keywords Alcohol use disorder · AUD · Tolcapone · COMT · Impulsivity · Decision-making

Introduction

The medical, social, and emotional costs of drug and alcohol abuse are extensive. The CDC estimates the economic burden of alcohol use disorder (AUD) to be in excess of 250 billion dollars per year in the USA alone (CDC 2019). Despite this widespread burden, the Food and Drug Administration has only approved three drugs to treat AUD: disulfiram, acamprosate, and naltrexone. Disulfiram, an irreversible inhibitor of alcohol dehydrogenase, primarily works by inducing unpleasant physiological effects if combined with alcohol and is therefore only effective in highly compliant patients. Acamprosate, a positive allosteric modulator, and naltrexone, a non-specific opioid receptor antagonist, are both relatively effective in increasing abstinence and reducing alcohol consumption, but they are also prone to unpleasant side effects that curb compliance and therefore limit their overall treatment efficacy. While these three therapeutics can attenuate alcohol consumption in certain subpopulations of AUD (Franck and Jayaram-Lindström 2013), they are infrequently prescribed, further curtailing their efficacy. These factors, along with the heterogeneity of the AUD population, suggest that the development of new compounds to reduce alcohol intake may benefit from directly addressing the cognitive and decision-related impairments that contribute to AUD.

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Published online: 02 July 2020

There is a strong relationship between decision-making deficits and AUD (Bechara 2005; Bickel et al. 2014; Phung et al. 2019). In particular, impulsive decision-making, as assessed by the discounting of delayed rewards, has been demonstrated to differentiate subjects with AUD from controls and to correlate with AUD severity (Mitchell et al. 2005). Previous data suggest that reduced dopaminergic tone in frontal brain regions contributes to both impulsivity (Kayser et al. 2012) and to problems with alcohol and drug abuse (Conner et al. 2010). Consistent with these findings, genetic variations in the dopamine-metabolizing enzyme catechol-O-methyltransferase (COMT), which represents an important pathway for degradation of cortical dopamine (Chen et al. 2004), have been linked to behavioral differences in drug and alcohol consumption and to impulsive decision-making (Boettiger et al. 2007; Schellekens et al. 2012). A single-nucleotide polymorphism (SNP) substitution from A to G in the COMT gene triggers a Met to Val substitution (Met158Val), which results in fourfold higher COMT activity and, via increased dopamine metabolism, a decrease in frontal dopamine tone (Schacht 2016). In keeping with this hypothesis, homozygotes for this Val substitution tend to exhibit heightened impulsivity compared with Met carriers in measures of impulsive choice (Boettiger et al. 2007).

Intriguingly, a brain-penetrant COMT inhibitor, tolcapone, has recently been shown to improve decision-making in healthy control subjects by increasing choice for larger but delayed rewards over smaller immediate rewards in more impulsive individuals (Kayser et al. 2012). As individuals suffering from AUD have difficulty with this type of impulsive choice (Mitchell et al. 2005), it follows that tolcapone might similarly improve decision-making in AUD subjects and thereby attenuate alcohol consumption. While tolcapone carries a black box warning due to its implication in the death of three patients with Parkinson's disease (PD), since the implementation of labeling restrictions in 1998, there have only been three reports of severe but reversible liver injury (Olanow and Watkins 2007). Although this safety profile is important to keep in mind when treating AUD subjects with tolcapone, applying the strict screening criteria from the updated labeling restrictions may allow tolcapone to be safely used in an AUD population. In addition, identifying COMT inhibition within the CNS as a mechanism for reducing alcohol consumption might stimulate the development of new compounds.

Here, we hypothesized that tolcapone would attenuate alcohol consumption and improve decision-making in subjects with AUD. In a randomized, double-blind, crossover design, we compared the effects on self-reported weekend alcohol consumption during a 5-day course of tolcapone versus placebo in a population of non-treatment-seeking alcohol drinkers meeting DSM-5 criteria for AUD. Additionally, alcohol consumption during a proof-of-principle laboratory bar paradigm was evaluated. Laboratory bar paradigms can utilize a controlled alcohol administration setting to assess effects of pharmacological agents on consumption; here, we modified the paradigm to pilot a group laboratory bar paradigm to create a more naturalistic setting for a social drinking population. In an effort to assess the cognitive contribution of alcohol consumption in this population, we also administered decision-making tasks during the laboratory sessions. Lastly, to explore whether individuals with different levels of COMT activity respond differently to a COMT inhibitor, subjects were genetically screened for the Met158Val COMT polymorphism. Consistent with our hypotheses, tolcapone reduced weekend alcohol consumption in a manner that correlated with reduced delay discounting across subjects. In contrast, and contrary to our predictions, no effects of tolcapone were seen in the laboratory bar.

Materials and methods

Experimental design

Subjects participated in a total of seven visits: screening, drug dispensation × 2, compliance × 2, and laboratory session × 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 the 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.

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 et al. 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-

Table 1 Demographics information of study participants

Gender	*n*	Percent
Males	32	58.2%
Females	23	41.8%
Age	*n*	Percent
21–24	21	38.2%
25–29	21	38.2%
30–34	10	18.2%
35–40	3	5.4%
Total	55	100%
Race and Ethnicities	*n*	Percent
Hispanic	8	14.5%
Non-Hispanic	47	85.5%
A. American Indian or Alaskan Native	1	1.8%
B. Asian	9	16.4%
C. Black or African American	2	3.6%
D. Native Hawaiian or Pacific Islander	1	1.8%
E. White	36	65.5%
2 or more of the above	6	10.9%
Total	55	100%

Table 2 Screening information of study participants

Measure	Mean (SD)	Range
Self-reported drinks/week at screening	21.3 (9.4)	10–52
Alcohol use disorders identification test	14.3 (5.6)	4–34
Barratt impulsivity scale	62.3 (10.1)	42–87
ICR % (on placebo)	56.6 (36.6)	0–99.3%
Education (in years)	15.2 (1.3)	12–20
Alcohol use disorder severity (DSM 5)	*n*	Percent
Mild	1	1.8%
Moderate	24	43.6%
Severe	30	54.5%

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 h 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 et al. 1993)) and the Barratt Impulsiveness Scale (BIS; (Patton et al. 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 h, we expect the drug reached steady-state at approximately 12.5 h (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 (Fig. 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 1×/day or more, 90.0% opened the MEMS cap 2×/day or more, and 59.1% opened the MEMS cap 3×/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 h 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

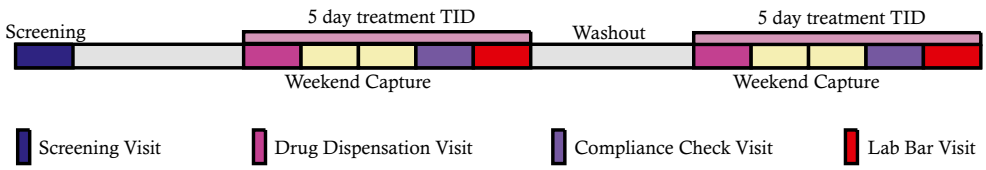

Fig. 1 Overview of study design. Subjects participated in a total of seven visits: screening, drug dispensing × 2, compliance × 2, and laboratory session × 2. Upon completion of the first randomized double-blind drug cycle and a washout, subjects were crossed over to complete the second drug cycle

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 et al. 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 and Mozayani 2007): $g = kg * r * BAC * 10$, where $r = 0.68$ for males and 0.55 for females, and where BAC = 0.04. Subjects were required to consume the priming drink within 15 min. 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 h session. Each drink was 1/2 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 h 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 h 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 et al. 2009). We calculated that, for a mean difference of 0.5 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 0.05 with a power of 0.80 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 attend the scheduled visit, and 3 subjects had positive urine drug screens at the first lab bar visit and ended their participation. Fifty 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.

Results

Demographics

Non-treatment-seeking subjects with a history of moderate to heavy alcohol consumption were recruited from the community. Data from 55 subjects (58.2% male, average age 26.2, SD 4.36) were included in the analyses. Demographic data is outlined in Table 1.

Weekend alcohol consumption

Total weekend alcohol consumption (Friday to Sunday) in non-treatment-seeking subjects was recorded each day for each drug cycle. Subjects demonstrate a small but statistically significant decrease in weekend alcohol consumption following tolcapone administration (Fig. 2, 13.35 ± 0.92 drinks on placebo vs. 11.78 ± 0.95 drinks on tolcapone, Cohen's d = − 0.225, t (54) = 2.05, p = 0.045, n = 55). There was no effect of the order of active study drug on weekend consumption (active study drug first = 12.88 ± 0.87 drinks versus second = 12.25 ± 1.01 drinks, t (54) = 0.81, p = 0.42, n = 55). Further division of subjects by COMT genotype did not reveal an additional contribution of allelic variation to the effect of tolcapone on drinking (F(2,52) = 0.57, p = 0.56, n = 16 Met/Met, 26 Met/Val, 13 Val/Val, respectively; data not shown).

Impulsive choice

There was no main effect of tolcapone on impulsivity as assessed by the impulsive choice ratio (ICR) in the delay discounting task (t (46) = −0.857, p = 0.396, n = 47; data not shown). Additionally, impulsivity as assessed by the BIS was not predictive of tolcapone's effect on ICR (t (46) = 0.977, p = 0.386, n = 47; data not shown). However, there was a positive relationship between the tolcapone effect (ICR on tolcapone; ICR on placebo) on delay discounting and its effect on alcohol consumption. Specifically, we find a significant correlation between the tolcapone effect on weekend drinking and the tolcapone effect on delay discounting, such that subjects with the greatest decreases in impulsive choice ratio (ICR) on tolcapone also reported the greatest decreases in alcohol consumption (Fig. 3a, r (45) = 0.40, p = 0.0053).

In an effort to determine whether there could be a genetic influence on tolcapone effects on drinking, we performed an

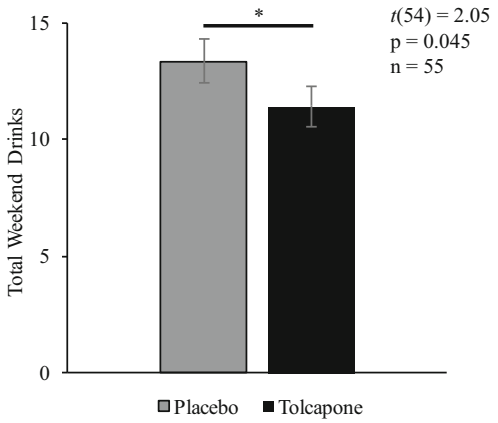

Fig. 2 Alcohol consumption. There was a significant decrease in weekend alcohol consumption following tolcapone administration. Means and SEM depicted for tolcapone and placebo drinking. 13.35 ± 0.92 drinks on placebo vs. 11.78 ± 0.95 drinks on tolcapone, Cohen's d = − 0.225, t (54) = 2.05, p = 0.045, n = 55

exploratory analysis to evaluate the effect of COMT genotype on changes in ICR following tolcapone versus placebo. We found that when subjects were divided by COMT genotype, subjects with presumptively greater frontal dopamine tone (Met/Met) were those most likely to decrease their impulsive choice on tolcapone (Fig. 3b, $F(2,44) = 3.35$, $p = 0.044$, $n = 13$ Met/Met, 21 Met/Val, 13 Val/Val, respectively). As noted above, however, this effect of genotype on change in ICR did not translate to an effect of genotype on change in weekend alcohol consumption.

Laboratory consumption

We were unable to detect an effect of tolcapone on the number of tray drinks subjects chose to consume in the laboratory paradigm following the priming drink (placebo drinks 2.82 ± 0.18, tolcapone drinks 2.58 ± 0.22, T = 1.336, $p = 0.188$, $n = 50$). Laboratory bar consumption tended toward an order effect, wherein subjects ordered more drinks during their first laboratory session than their second, irrespective of drug cycle (first 2.84 ± 0.17, second 2.56 ± 0.22, $T = 1.568$, $p = 0.123$, $n = 50$). This pattern may have been influenced by participants' subjective experience at the end of the first laboratory bar session, as several subjects commented on the wait time necessary to be sober enough for dismissal from the study site (see Discussion). During the drinking sessions, we also compared latency to first sip (placebo latency 78.1 ± 12.0 s, tolcapone latency 67.3 ± 11.3) and total grams of alcohol consumed (placebo 77.2 ± 7.8 g, tolcapone 72.6 ± 8.6 g) and did not find a difference between tolcapone and placebo.

Medication tolerability

The 5-day 100 mg TID tolcapone dose was well tolerated. Side effects data were tabulated for all subjects who were dispensed drug, including subjects who withdrew prior to study completion. Subjects endorsed a low average rate of side effects at baseline prior to initial drug administration for each medication cycle (placebo 0.66 ± 0.15 and tolcapone 0.48 ± 0.12), which significantly increased during both medication cycles (2 × 2 RM ANOVA baseline vs. medication cycle: $F(1,119) = 26.1$, $p < 0.0001$), with no significant difference between placebo and tolcapone side effects reported (placebo 1.51 ± .28 and tolcapone 1.63 ± .33; 2 × 2 RM ANOVA tolcapone vs placebo: $F(1,119) = 0$, $p = 1$). A total of 11 subjects reported a "moderate" or "severe" side effect (4 were on study drug). All adverse events were followed by our staff nurse practitioner until fully resolved. The "moderate to severe" side effects reported by the 4 subjects taking study drug were light-headedness, lethargy, fatigue, and decreased appetite, and the study clinician determined that these symptoms could possibly be related to study drug. As per FDA guidance, these "adverse events" were then assigned a severity on a 1–4 scale indicating the extent to which the symptom interfered with daily activity. All reported events were assigned a 1 on this scale (i.e., did not interfere) with the exception of lightheadedness, fatigue, and/or lethargy, reported by two subjects, which were assigned a severity grading of 2 (i.e., interfered but did not require treatment beyond over the counter medicine). All of these symptoms resolved without specific intervention and did not result in subject discontinuation.

Discussion

Here we show that the COMT inhibitor tolcapone attenuates weekend alcohol consumption in a group of non-treatment-seeking participants meeting DSM-5 criteria for alcohol use disorder (AUD). We additionally find that there is a significant positive correlation between the tolcapone-induced decrease in weekend alcohol consumption and the tolcapone-induced decrease in impulsive choice as assessed by a delay discounting task (DDT). In contrast, we did not find an effect of tolcapone on alcohol use during the laboratory bar protocol, potentially because of unforeseen consequences resulting from study procedures. These findings are in keeping with previous data demonstrating a link between decision-making deficits and AUD (Bechara 2005; Mitchell et al. 2005), and

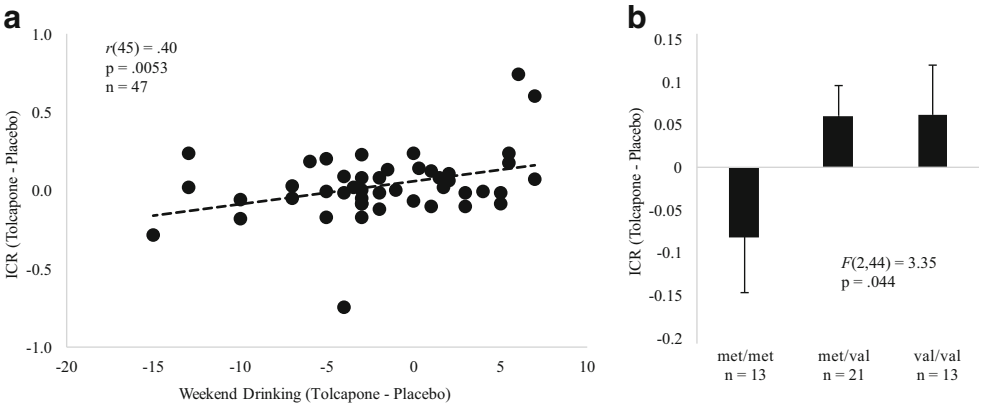

Fig. 3 Impulsive choice. There was a significant positive correlation between the tolcapone effect on weekend drinking and the tolcapone effect on delay discounting (**a**), $r(45) = 0.40$, $p = 0.0053$, as well as an overall effect of genotype on change in ICR following tolcapone (**b**), means and SEM depicted for each genotype, $F(2,44) = 3.35$, $p = 0.044$, $n = 13$ Met/Met, 21 Met/Val, and 13 Val/Val, respectively

they lend further credence to the theory that impulsive decision-making, as assessed by the discounting of delayed rewards, may also exacerbate alcohol use. While this proof-of-principle study provides intriguing data, a larger clinical study is needed to thoroughly assess whether changes in extended drinking behavior correlate with decision-making when dopaminergic tone is pharmacologically enhanced.

Importantly, these findings were seen despite the use of a non-treatment-seeking population with AUD. The use of a non-treatment-seeking population is fundamentally conservative: it permits the assessment of changes in drinking behavior with fewer confounding factors such as desire to achieve abstinence, or efforts to seek approval from providers, and is also consistent with NIAAA Council recommendations for experimental alcohol administration. Thus, although the reported effect of tolcapone on alcohol consumption is modest, this finding comes from a population in which it is more challenging to identify a drug effect (Lee et al. 2019; Ray et al. 2017; Rohn et al. 2017). Additionally, by establishing a direct correlation between reduction in weekend drinking and a decline in delay discounting on tolcapone, this study provides strong support for a link between impulsivity and addictive behaviors, and it demonstrates that they are both influenced by tolcapone-mediated changes in cortical dopamine tone. In a treatment-seeking population, which typically displays higher levels of impulsivity (Rohn et al. 2017), this correlation and the overall effect of tolcapone on drinking may be enhanced. This finding therefore provides a clinically significant indicator of mechanism. Specifically, because these changes correlate with reductions in impulsivity in individual subjects, these data provide direct support for the broader idea that improving a cognitive phenotype can improve risky behaviors in the real world.

These findings also speak to the importance of individual differences. Although we observed a beneficial behavioral effect of tolcapone in many subjects (decreased alcohol consumption and decreased impulsive choice), it is detrimental in others (increased alcohol consumption and increased impulsive choice; Fig. 3A). While this difference is undoubtedly dependent on a number of factors, it is generally understood that dopamine effects manifest as an inverted U-shaped curve, in which either too much or too little dopamine can be detrimental to executive functions that contribute to decision-making (Cools 2008). Therefore, the enhancement of frontal dopamine tone by tolcapone could have either a positive or negative behavioral effect, depending on an individual's baseline dopamine tone. Future clinical trials would clearly benefit from further efforts to identify cognitive predictors of alcohol treatment response, such as a tolcapone-mediated decline in impulsivity on a delay discounting task.

Consistent with the above ideas, the ability of tolcapone to impact behavioral processes has previously been linked to the functioning of the prefrontal dopamine system (Volkow and Baler 2015). Past data indicate that reduced dopaminergic tone in frontal brain regions contributes to both impulsivity (Kayser et al. 2012) and to problems with alcohol and drug abuse (Conner et al. 2010). Variations in the dopamine-metabolizing enzyme catechol-O-methyltransferase (COMT) have been linked to behavioral differences in drug and alcohol consumption and to impulsive decision-making (Boettiger et al. 2007; Schellekens et al. 2012), and the administration of a single dose of tolcapone has previously been shown to attenuate impulsive choice in healthy control subjects (Kayser et al. 2012). While we demonstrated a main effect of tolcapone on alcohol consumption, we were unable to replicate the previously reported effect of a single dose of tolcapone on impulsive choice (Kayser et al. 2012). This disparity may be due to methodology differences including the subject population, drug dose, dosing regimen, and setting (individual versus group).

Exploratory analysis of COMT Met158Val genotype showed that, while this polymorphism did not explain the reduction in alcohol consumption in individual subjects, it did correspond with the effectiveness of tolcapone in altering the impulsive choice ratio (ICR). Specifically, subjects with the Met/Met genotype, which is presumptively associated with higher cortical dopamine tone, show a decline in impulsivity on tolcapone (Fig. 3b). If replicated, one possible explanation for the decrease in impulsivity in Met/Met rather than Val/Val subjects is that the Met/Met genotype endows subjects with a greater tendency to compute the value of future rewards in cortical regions, and therefore, tolcapone may be better able to augment these pre-existing representations in Met/Met subjects. In support of this theory, a previous study (Kayser et al. 2015) found that subjects with presumptively higher frontal dopamine tone (Met/Met) showed greater increases in exploration following the administration of tolcapone than did subjects with presumptively lower frontal dopamine tone (Val/Val).

Additionally, we did not detect an effect of tolcapone on alcohol consumption in our group laboratory bar paradigm. The group paradigm revealed a number of confounding variables that may have impacted subjects' behavioral choices differently between the two sessions. As noted in the Results section, we found a trend-level effect of study session, with study subjects drinking less at the second study visit. Because subjects learned after the first lab session that they could not leave in an impaired state (BAC > 0.04), they consumed less alcohol during the second lab session in order to be dismissed sooner. In addition, study staff noted overhearing discussions between subjects during the laboratory session that revealed that social influence within the group served to reduce (or increase) consumption. Though this paradigm did not demonstrate differences in consumption on tolcapone, the confounding variables that we observed serve to reinforce the significant contribution of social interactions to alcohol consumption

behaviors and to the need to take these into consideration when designing future laboratory studies.

With respect to tolcapone itself, the current laboratory study also demonstrates the potential safety and efficacy of a short course of TID tolcapone in otherwise young, healthy individuals with AUD. In this population, no discernable liver-related side effects were reported in conjunction with tolcapone administration. While the mechanism by which tolcapone induces hepatotoxicity is still unknown, in considering an alcohol-consuming population, it is important to note that only non-substantive differences in tolcapone pharmacokinetics have been seen in individuals with moderate cirrhosis or hepatitis (Jorga et al. 1998). As liver enzyme monitoring is required for those on long-term tolcapone dosing regimens for Parkinson's disease, it is likely that similar liver enzyme monitoring would be an appropriate measure to ensure the safety of AUD patients. Of course, if the current results can be replicated, they would reinforce the need to develop additional brain-penetrant inhibitors of COMT that might not share this need for monitoring of liver function.

In conclusion, the current experiment shows that the centrally acting COMT inhibitor tolcapone induces a statistically significant attenuation of weekend alcohol consumption in non-treatment-seeking AUD subjects. Importantly, the effects of tolcapone on drinking were significantly correlated with changes in impulsive decision-making, such that subjects with the greatest decrease in impulsive choice on tolcapone also reported the greatest decrease in alcohol consumption. This combination of improved decision-making and attenuated alcohol consumption supports the potential use of centrally acting COMT inhibitors such as tolcapone for AUD while providing proof-of-principle evidence for treatment strategies designed to target cognitive phenotypes.

Acknowledgments The authors thank Valeant Pharmaceuticals for the generous donation of study drug.

Funding information This study was supported by the Department of Defense funds for Alcohol and Substance Abuse Disorders Research Program (W81XWH-12-2-0048 & W81XWH-13-2-0075) awarded to JMM. ASK and JMM were supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (R01 AA026587).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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