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## The *OPRD1* rs678849 variant influences outcome of disulfiram treatment for cocaine dependency in methadone-maintained patients

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### Abstract

**Objective:** Prior research demonstrated that the  $\delta$ -opioid receptor (*OPRD1*) rs678849 variant influences opioid use in African Americans treated with methadone. We examined whether this variant moderated cocaine and opioid use in our clinical cohort of methadone and disulfiram treated recipients.

**Methods:** Cocaine and opioid co-dependent patients were stabilized for two weeks on methadone and subsequently randomized into groups treated with either methadone+placebo ( $n = 37$ ) or methadone+disulfiram (250 mg/day,  $n = 33$ ) for 12 weeks.

**Results:** A drop in cocaine positive urines was found in the *OPRD1* CC genotype group compared to T-allele carrier patients treated with methadone+disulfiram ( $P < 0.0001$ ), but not in the methadone+placebo group. No difference in opioid positive urines were found among each genotype group in either treatment group.

**Conclusion:** These findings suggested that rs678849 genotype may predict treatment response of disulfiram for cocaine use in patients with co-occurring opioid and cocaine dependence.

### Keywords

Disulfiram; methadone; polymorphism; cocaine; opioid; *OPRD1*

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Conflicts of interest

There are no conflicts of interest.

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## Introduction

Opioid dependence (OD, as defined in DSM-IV) is a chronic disease that accounted for 28% of all drug abuse treatment admissions in 2015 (SAMHSA-TEDS, 2018) and imposed an annual economic burden of 56 billion dollars in the United States in 2007 (Birnbaum et al., 2011). Cocaine dependence (CD) co-occurs with opioid dependence in 30–50% of methadone-maintained populations (Grella et al., 1997). This comorbidity worsens most outcomes, resulting in decreased treatment completion, increased relapse, and poorer mental health outcomes (Villano et al., 2002, Bovasso and Cacciola, 2003, Tzilos et al., 2009, King et al., 2014, White et al., 2014, Oviedo-Joekes et al., 2015). As such, there is a critical need for clinical trials to examine the effectiveness treatment of OD/CD comorbidity. Although there are no FDA approved drugs for OD/CD nor CD alone (Kenna et al., 2007), some drugs have demonstrated efficacy for both disorders. Methadone is primarily used for treatment of OD, but reduces co-occurring cocaine use when given in doses > 60 mg (Faggiano et al., 2003, Peles et al., 2006). Disulfiram, when given with methadone in opioid users, reduces cocaine, but not opioid positive urines in opioid users (Petrakis et al., 2000, Kosten et al., 2013). Many suspect that disulfiram prevents relapse through its inhibition of dopamine  $\beta$ -hydroxylase, which decreases conversion of dopamine to norepinephrine, thus lowering norepinephrine tone and reducing stress-related reinstatement of cocaine use (Gaval-Cruz and Weinshenker, 2009).

Methadone treatment for OD acts through the opioid receptor family, which includes the  $\mu$ -opioid receptor (MOR),  $\kappa$ -opioid receptor (KOR), and  $\delta$ -opioid receptor (DOR). Methadone acts as a full agonist at MOR at typical treatment doses, resulting in a release of dopamine which produces rewarding effects similar to endogenous and illicit opioids (Kreek et al., 2005). Methadone binds to KOR and DOR at much lower affinities, and likely does not illicit the typical dysphoria from KOR activation or analgesia from DOR activation (Kristensen et al., 1995, Chavkin, 2011).

Despite not being activated by methadone, DOR function may play an important role in the treatment of co-occurring CD/OD, as evidenced by animal studies that demonstrate DOR's role in response to cocaine and tolerance to morphine (Unterwald et al., 1993, Zhu et al., 1999, Nitsche et al., 2002). Methadone may affect cocaine use through receptor heterodimers that DOR forms with MOR. The summation of opioid signaling by heterodimers of DOR and MOR may be an understudied part of opioid signaling, as these heteromers activate cell signaling pathways differently than either receptor alone *in vitro* (Kabli et al., 2014).

Approximately 25–35% of methadone-maintained patients have opioid-positive urine drug screens during treatment, even with adherence to methadone and supplemental psychosocial treatments (Zhang et al., 2013, Nielsen et al., 2016). These outcomes may be explained by genetic background, as heritability of illness is 70% in CD and 50% in OD (Khokhar et al., 2010). Variants in opioid receptor genes have been associated with CD, OD, and overall risk of substance use disorders (Yuferov et al., 2010, Levran et al., 2012, Schwantes-An et al., 2016).

The single nucleotide polymorphism (SNP) rs678849 is located in the first intron of *OPRD1*. The *OPRD1* variant rs678849 may be important for examining the effect of genotype on cocaine and opioid abuse. The CC genotype of rs678849 has been found to be associated with response to buprenorphine and methadone treatment of OD in African Americans (AA), but not in EAs (Crist et al., 2013a). Those participants carrying the CC genotype responding better to buprenorphine but worse to morphine than those carrying a T allele. In European American (EA) females, two other *OPRD1* variants, rs581111 and rs529520, were found to be associated with treatment response to treatment of OD with methadone or buprenorphine (Clarke et al., 2014). Crist et al., also found that during a 14-week treatment trial with topiramate *OPRD1* rs678849 T-allele carriers in cocaine- and alcohol-dependent AAs used less cocaine than did those with the CC genotype (Crist et al., 2016). These results have yet to be replicated in a multi-ethnic cohort and have not specifically tested disulfiram as a pharmacotherapy, but suggest that T-allele carriers respond better to cocaine pharmacotherapy.

The aims of this study were two-fold. First, since the *OPRD1* rs678849 variant is associated with treatment response to methadone pharmacotherapy for OD, we hypothesized that this variant also might be associated with disulfiram treatment in CD participants. We expect that T-allele carriers treated with methadone+disulfiram will have fewer cocaine positive urines than those patients having the CC genotype. Secondly, this study aimed to replicate and confirm the association of the *OPRD1* rs678849 variant with response to medication-assisted treatment of OD/CD patients from a multi-ethnic cohort. We hypothesized that methadone-maintained patients with a CC genotype will have fewer opioid positive urines than T-allele carriers.

## Material and methods

### Participants

From 2005–2006 and 2006–2008, OD/CD patients ( $n = 93$ ) stabilized on methadone maintenance at Yale University ( $n = 40$ ) and Baylor College of Medicine ( $n = 53$ ), respectively, were evaluated during a two-week screening period. Patient screening included physical examination and psychiatric interview with the MINI (English Version 5.0.0, July 1, 2006) (Sheehan et al., 1998) and the ASI (McLellan et al., 1992) to confirm DSM-IV-TR OD and CD diagnoses. DSM-IV-TR was used in our analyses as this was the classification in place during the patients' enrollment. This study used DSM-IV-TR for OD and CD diagnosis, as this was the standard for diagnosis during the participants enrollment (APA, 2000). DSM-5 was introduced in 2013 and modified the classifications of substance use disorders (SUDs) (APA, 2013). Previously in DSM-IV, SUDs were classified as substance use or substance dependence, with the latter classification having a higher degree of severity. DSM-5 combined these two classification to create the category SUD. In addition, the criterion of legal problems was deleted from DSM-V and replaced with cravings or a strong desire or urge to use a substance. SUD also is classified on the basis of severity, i.e., mild, moderate, or severe in DSM-V.

Patients were retained in the study if they had at least one urine sample positive for cocaine, and continued treatment and follow-up. Women of childbearing age were retained provided

they agreed to use adequate contraception and agreed to monthly pregnancy tests. Patients were excluded for current diagnosis of other drug and alcohol dependence (other than tobacco), acute or unstable medical illness, history of severe mental illness (such as psychosis, schizophrenia, or bipolar disorder), current suicidality, a positive urine pregnancy test for women, or inability to read and understand the consent form. This consent, as well as specific consent for genetic studies, was signed by all screened patients, and approved by Institutional Review boards of both institutions, and the Research and Development Committee of the Michael E. DeBakey Veterans Affairs Medical Center. Ninety-three patients were screened and 74 were included in the study. After applying exclusion criteria, the 74 patients were of African American ( $n = 9$ ), Hispanic ( $n = 8$ ), and Caucasian ( $n = 57$ ) ethnicity as determined by self-report. Participants had a mean age of 39 years old ( $SD = 10.4$ ) and were mostly white males (64%) (Table 1). Participants had abused cocaine for a mean of 12 years ( $SD = 8.1$ ) and heroin for a mean of 9 years ( $SD = 9.2$ ). All 74 patients were treated with methadone. Patients were randomly assigned into the methadone+placebo group or methadone+disulfiram treatment group. The final sample consisted of 70 participants with genotype data for *OPRD1* rs678849. Among the genotyped participants, there were 25 with the CC, 28 with the CT, and 17 with the TT genotype.

### Study design

Study participants were stabilized on methadone maintenance at 60 mg per day for two weeks. Methadone dose started at 25 mg per day and increased 5 mg per day until patients achieved a 60 mg per day maintenance dose. Patients then were assigned randomly to methadone+placebo or methadone+disulfiram treatment groups and treated for ten weeks. The disulfiram (250 mg daily) was dissolved into the patient's daily methadone dose to assure medication compliance. Individual manualized cognitive behavioral therapy (Carroll, 1997) was provided weekly to all participants. Supervised urine samples were obtained thrice weekly and tested for illicit opioids and cocaine metabolites as described previously (Nielsen et al., 2012).

### Genotyping & statistical analyses

DNA purification, genotyping, and statistical analyses were performed as previously described (Nielsen et al., 2012, Kosten et al., 2013). Briefly, we used the Gentra Puregene Buccal Cell Kit (Qiagen, Valencia, CA), following the manufacturer's recommendations, to isolate DNA using from pelleted buccal cells that were obtained by the centrifugation of 10 ml Scope® mouthwash that was used to rinse the subject's mouth for 60 seconds.

Genotypes were determined using a 5'-fluorogenic exonuclease assays (TaqMan®, Applied Biosystems, Foster City, CA). The *OPRD1* rs678849 variant was genotyped using the TaqMan® primer-probe sets (Applied Biosystems) assay ID C\_11264519\_1. PCR amplifications were performed using Platinum® quantitative PCR SuperMix-UDG (Invitrogen, Carlsbad, CA) on a GeneAmp® PCR system 9700 (Applied Biosystems).

A repeated-measures analysis of covariance (ANCOVA) was used to analyze the number of cocaine- or opioid-positive urines over the total number of samples (six) for each two-week period. All analyses were corrected for any possible confounding effects, by including the

proportion of each subject from the founder populations and sex as covariates in the model. Data from the methadone+disulfiram treatment group was compared to the methadone+placebo group over time to determine if the effect of either treatment (methadone+placebo or methadone+disulfiram) is moderated by the rs678849 *OPRD1* using R version 2.9.1 (R\_Development\_Core\_Team, 2009). Genotypes CT and TT were grouped as in the study by Crist et al. (Crist et al., 2013b). We compared condition (methadone+placebo or methadone+disulfiram), *OPRD1* genotype (0 = CC genotype, 1 = CT and TT genotypes), time (each two-week period), and interactions between condition and time, and between condition and genotype. We compared condition (disulfiram or placebo), *OPRD1* genotype (0=CT/TT genotype, 1=CC genotype), time (each 2-week period), and interactions between condition and time and between condition and *OPRD1*. We analyzed all individuals who had complete data ( $n = 55$ ) and unbalanced repeated measures ANCOVA for all genotyped individuals ( $n = 70$ ). The two analyses yielded similar results; therefore, all analyses were conducted with all genotyped individuals ( $n=70$ ). ANCOVA and  $\chi^2$  tests also was used to analyze demographic and MINI/ASI data.

Population structure was determined by genotyping ten ancestry informative markers (AIMs) and comparing our cohort against CEPH-HGDP samples (1,035 subjects of 51 populations) as previously described (Nielsen et al., 2012, Kosten et al., 2013). Lao et al have shown this approach obtains 94.6% of the maximum informativity value (Lao et al., 2006). Sex was confirmed by genotyping SRY (Kosten et al., 2013). Sex, recruitment site, and population structure (three of the four population structure values) were run as covariates in each statistical model. Corrections for multiple testing were performed to evaluate experiment-wise significance by applying the Bonferroni correction for the four analyses conducted (methadone+placebo versus methadone+disulfiram group and the CC genotype group versus T-allele carriers for both cocaine and opioid use. This study was designed as an evaluation of the role of *OPRD1* rs678849 under these four conditions with experiment-wise significant being  $P < 0.05/4 = 0.013$ ). Effect size was calculated as a partial eta-squared statistic using condition or variant variance over residual variance. The three general cut-offs for effect size are the following: a large effect is 0.14, a medium effect is 0.06, and a small effect is 0.01 (Cohen, 1988). Hardy-Weinberg equilibrium was calculated for the *OPRD1* rs678849 variant and resulted in non-significant  $p$ -values indicating that the genotypes were observed in the expected ratios ( $P = 0.113$ ).

## Results

### Cocaine Treatment Outcomes

The overall cohort showed a disulfiram treatment effect ( $F = 16.1$ ;  $df = 1,364$ ;  $P < 0.0001$ , with an effect size of 0.04) similar to results we had reported previously (Kosten et al., 2013). Positive cocaine urine rates decreased from 79% during the baseline two weeks to 62% for the methadone+disulfiram group and to 75% for the methadone+placebo group during the last two weeks of treatment.

The 70 patients that were genotyped for the *OPRD1* alleles were divided into two groups based on their *OPRD1* rs678849 genotypes. Patients with one or two T alleles (CT and TT genotypes; T-allele carriers) were compared to those with a CC genotype. As shown in

Figure 1, disulfiram reduced cocaine positive urines more than any other group when used in CC genotype patients treated with methadone. There was a treatment by genotype interaction ( $F = 8.89$ ;  $df = 1,364$ ; experiment-wise  $P = 0.0001$ , with an effect size of 0.05) on cocaine-positive urines.

Patients with the CC genotype had better outcomes with methadone+disulfiram treatment than with methadone+placebo treatment ( $F = 27.7$ ;  $df = 1,127$ ; point-wise  $P < 0.0001$ , experimental-wise  $P < .001$ , with an effect size of 0.22). In these CC participants, the cocaine positive urines in the methadone+disulfiram group dropped from 77% at week 1–2 to 47% at week 11–12 for a 39% drop, while the cocaine positive urines in the methadone+placebo group showed little change of 86% to 84% over the same period (10%). Those patients with the CT/TT genotype showed no difference in cocaine positive urines between methadone +disulfiram and methadone+placebo treatments. For the CT/TT patients, the cocaine positive urines in the methadone+disulfiram group dropped from 81% to 65% (20% drop), while the methadone+placebo group showed little change from 76% to 71% (10% drop).

### Opioid treatment outcomes

No association was found with experiment-wise significance for differences in treatment outcome in opioid-positive urines. Neither genotype nor disulfiram/placebo treatment groups showed main effects on opioid-positive urines for the combined cohort.

### Discussion

The first aim of this study was to replicate the findings of Clark's, who found a decrease in opioid-positive urines in AA participants carrying in *OPRD1* rs678849 GG participants (Crist et al., 2013a). Our results did not support Clark's finding, either methadone alone, or with methadone plus disulfiram.

Our second aim was to examine the role of *OPRD1* rs678849 in moderation of disulfiram treatment response for CD in a multi-ethnic population. In the CC, but not in the T-allele carrier participants, the methadone patients when treated with disulfiram decreased the number of cocaine-positive urines while in those treated with placebo had minimal decrease in cocaine-positive urines. In contrast, the T-allele participants did better than CC carriers in a clinical trial on CD with topiramate (Crist et al., 2016). This lack of a precise replication may have resulted from multiple factors. First, not only did the cocaine pharmacotherapies differ, but also the comorbid substance dependencies differed, alcohol with topiramate and opioid with disulfiram. Second, the underlying mechanisms for both medications are not direct effects on DOR and are quite different between the enzyme inhibition of disulfiram, and the glutamate and gamma amino butyrate action of topiramate. Thus, indirect pharmacogenetic effects on the DOR and cocaine use might be the opposite for these two medications in different comorbid patient populations.

We previously examined eight other pharmacogenetic associations in this clinical trial and found a genotype dependent effect on treatment response for polymorphisms in the following genes: *α1A-adrenoceptor (ADRA1A)*, *dopamine β-hydroxylase (DBH)*, *ankyrin repeat and kinase domain-containing 1 (ANKK1)*, *dopamine receptor D2 (DRD2)*,

*dopamine transporter (SLC6A3), 5,10-methylene tetrahydrofolate reductase (MTHFR), serotonin-transporter-linked polymorphic region (SLC6A4, 5-HTTLPR), and tryptophan hydroxylase 2 (TPH2)* (Nielsen et al., 2012, Spellicy et al., 2012, Kosten et al., 2013, Shorter et al., 2013, Spellicy et al., 2013, Kampangaew et al., 2019). These multiple associations highlight the pleiotropic way methadone+disulfiram can improve cocaine treatment outcomes in OD/CD co-dependent patients.

The *OPRD1* rs678849 locus is associated with a function that might affect disulfiram and methadone treatment of CD/OD. Crist et al., reported that the T-allele of rs678849 in intron 1 of *OPRD1* is located in a binding site for USF2 (Crist et al., 2013a), a transcription factor that may regulate how much DOR is transcribed from the *OPRD1*. The C-allele at this site abolishes USF2 binding and may reduce DOR levels. Reduced DOR signaling enhances chronic methadone's effects of internalizing and degrading MOR (Zhu et al., 1999, Nitsche et al., 2002, He et al., 2011).

Genetic variations in the *OPRD1* gene appear to be centrally involved in the vulnerability to develop and maintain addictions, and are involved in the efficacy of their treatment. The *OPRD1* variants rs2236861, rs2236857 and rs3766951 have been found to be associated with vulnerability to develop opioid addiction. The *OPRD1* intron 1 variant rs508448 (Gao et al., 2017) and a haplotype of the *OPRD1* intron 1 variants rs2236857 and rs581111 were found to be associated with risk for heroin dependence (Nelson et al., 2014) while the *OPRD1* exon 1 variant rs1042114 was associated with OD (Zhang et al., 2008). Recently, two *OPRD1* variants, rs204047 and rs797397, were found to be associated with plasma R, S-methadone concentrations (Fang et al., 2020). The *OPRD1* variant rs204047 (Fang et al., 2020) and rs529520 (Luo et al., 2017) was found to be related to methadone dosage among participants in methadone maintenance treatment (MMT).

In additional studies, the *OPRD1* variant rs204047 was associated with diastolic blood pressure and heart rate in MMT patients (Fang et al., 2020). Furthermore, *OPRD1* variants rs9322447 and rs609148 had a role in personality traits such as Openness and the variant rs2234918 with Agreeableness (Luo et al., 2008). A role of the *OPRD1* variant rs569356 was observed in anorexia nervosa (Brown et al., 2007). Hence, our finding an association with rs678849, although it has a small effect size, is in line with these other associations of *OPRD1* variants.

This study has several limitations. These results may be less generalizable to cocaine abusers that are not opioid dependent. Additionally, the effect size of the most significant findings is small, but consistent with most pharmacogenetic studies. Overall, efforts to replicate pharmacogenetics studies often are hampered by small effect sizes, small samples size, and the constraints of randomized clinical trials. These limitations lead to replication rates as low as 3.4%, which is similar to genome-wide association study (GWAS) replication rates (Aslibekyan et al., 2013). Many academic pharmacogenetic studies on new pharmacotherapies involve moderately sized groups. These human pharmacotherapy studies require substantial energy in terms of cost and time to perform. However, promising candidate pharmacotherapies often will be followed up with larger studies for confirmation and for developing FDA approved pharmacotherapies of cocaine addiction by matching

genetically identified patients with appropriate medications. Given that medication assisted treatment for co-occurring substance use disorders has not been successful, further research using genetic backgrounds to guide medication-assisted treatment may allow pharmacotherapy to be personalized, thereby improving outcomes.

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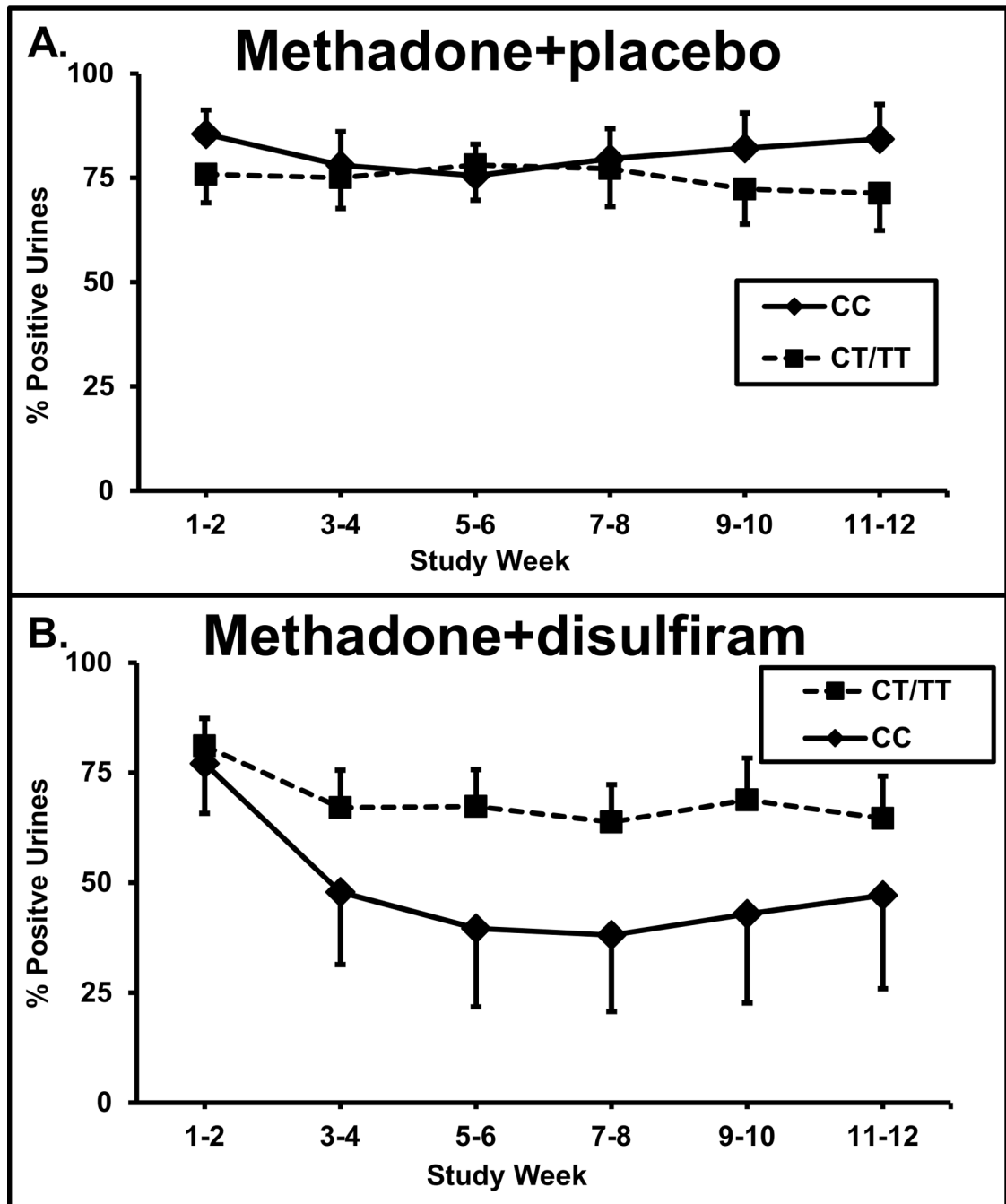
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**Fig. 1.** Percentage of cocaine positive urine toxicology screens for two-week time blocks across the 12-week trial for the methadone+placebo treatment group. A. Percentage of cocaine positive urine toxicology screens in the methadone group with the CC genotype (diamond symbols, solid line,  $n = 17$ ) and those with CT/TT genotypes (square symbols, dashed lines,  $n = 20$ ) are displayed. Standard error bars are shown at each time point. B. Percentage of cocaine positive urine toxicology screens when treated with methadone+disulfiram (dashed line) or methadone+placebo (solid line) in those with the CT/TT genotype (square symbols) and

those with CC genotypes (diamond symbols) are shown. Standard error bars are shown at each time point.

**Table 1.**Demographic and clinical characteristics by treatment and *OPRD1* genotype.

Characteristic	Methadone+placebo		Methadone+disulfiram	
	CC	CT/TT	CC	CT/TT
N	17	20	8	25
% Male	65	65	75	60
% Caucasian	59	85	63	84
% African American	29	10	13	4
% Hispanic	12	5	25	12
Age, Years (SD)	39 (12)	40 (10)	40 (11)	38 (10)
ASI Employed	5 (3)	3 (3)	4 (3)	3 (3)
Alcohol Last 30 Days	3 (4)	3 (5)	1 (2)	2 (3)
Alcohol, Years	4 (7)	5 (7)	3 (5)	3 (6)
Intoxicated Last 30 Days	0 (0)	0 (1)	0 (0)	0 (2)
Intoxicated, Years	0 (0)	3 (6)	3 (5)	3 (6)
Heroin Last 30 Days	23 (13)	11 (13)	19 (15)	10 (14)
Heroin, Years	10 (12)	10 (7)	12 (10)	9 (8)
Methadone, Last 30 Days	8 (12)	19 (14)	14 (15)	13 (15)
Methadone, Years	2 (7)	2 (4)	2 (4)	3 (7)
Cocaine Last 30 Days	18 (10)	19 (8)	16 (12)	17 (10)
Cocaine, Years	15 (10)	14 (6)	10 (7)	9 (7)
Marijuana Last 30 Days	3 (7)	2 (7)	1 (1)	1 (2)
Marijuana, Years	6 (9)	5 (9)	7 (7)	7 (8)
Illegal drug, Last 30 Days	4 (9)	5 (11)	7 (13)	4 (10)