Published in final edited form as:

J Addict Med. 2013 ; 7(4): 243–248. doi:10.1097/ADM.0b013e3182928e02.

Effects of Disulfiram on QTc Interval in non-Opioid Dependent and Methadone-Treated Cocaine Dependent Patients

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Abstract

Objectives—Methadone and cocaine are each known to prolong the QTc interval, a risk factor for developing potentially fatal cardiac arrhythmias. Disulfiram, often administered in the context of methadone maintenance to facilitate alcohol abstinence, has been shown to have some efficacy for cocaine dependence. Disulfiram has differential effects on cocaine and methadone metabolism, but its impact on methadone- or cocaine-induced changes in QTc interval is unclear. Thus, the effects of disulfiram on QTc interval in a subset of cocaine dependent patients participating in a 14 week, randomized, double blind, placebo-controlled clinical trial of disulfiram was prospectively determined.

Methods—Opioid dependent participants were inducted onto methadone (wks 1-2; MT) and both MT and nonopioid dependent (UT) participants were randomized to receive disulfiram (wks 3-14) at one of the following doses: 0, 250, 375, or 500 mg/day. Electrocardiograms (ECGs) were obtained prior to study entry and during weeks 2 and 4.

Results—Complete QTc interval data in 23 MT and 18 UT participants were analyzed. QTc interval tended to be higher in MT relative to UT dependent participants, regardless of disulfiram dose and time point, but disulfiram did not differentially alter QTc interval. QTc interval was, however, significantly greater in participants with recent cocaine use than those with no recent use.

Conclusions—These results suggest that cocaine use and possibly MT status, but not disulfiram, are risk factors for QTc prolongation.

Keywords

clinical trial; cocaine dependence; disulfiram; opioid dependence; QTc prolongation

Cocaine dependence is a serious public health problem. The United States is the world's largest cocaine market, and up to one fifth of those who have used cocaine in the last year in the US met Diagnostic and Statistical Manual criteria for dependence (Chawla, 2010). Furthermore, cocaine is associated with approximately 40% of drug-related deaths in the

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Conflicts of Interest: For all authors, none were declared.

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USA in 2008. The United Nations considers cocaine to be second only to opiates as the most problematic drug of abuse in the world (Chawla, 2010). One recent meta-analysis suggests the Standardized Mortality Rates are four-to-eight times higher in cocaine users than in age and sex-matched peers in the general population (Degenhardt et al., 2011). Pharmacotherapy for the treatment of cocaine dependence is lacking, and an agent that is able to facilitate abstinence for cocaine abusers is being sought (Sofuoglu & Kosten, 2006).

Comorbid cocaine dependence is also a major problem among methadone maintenance programs, where rates of cocaine use may reach 25-50% (Condelli, Fairbank, Dennis, & Rachal, 1991; Wallner et al., 2008). Cocaine use during methadone maintenance has been associated with medical (MacGowan et al., 1997), psychiatric (El-Bassel et al., 2004; Grella, Anglin, & Wugalter, 1995) and legal (Grella, et al., 1995; Hunt, Spunt, Lipton, Goldsmith, & Strug, 1986) problems. Moreover, cocaine use (Erwin & Deliargyris, 2002; Levin, Copersino, Epstein, Boyd, & Gorelick, 2008; Magnano et al., 2006) and methadone maintenance (Krantz, Lowery, Martell, Gourevitch, & Arnsten, 2005; Martell, Arnsten, Krantz, & Gourevitch, 2005; Wallner, et al., 2008) are independent risk factors for QTc prolongation. QTc prolongation describes an abnormal lengthening in the interval between the QRS complex and the T wave in electrocardiography, reflecting an increased period of ventricular depolarization and repolarization (Kautzner, 2002). Prolonged QTc interval is associated with cardiac complications such as Torsade de Pointes, ventricular tachycardia, and sudden cardiac arrest (Gupta, Lawrence, Krishnan, Kavinsky, & Trohman, 2007). These findings suggest that effects on cardiac functions of potential pharmacotherapies for treating cocaine dependence, particularly in the context of methadone maintenance, should be ascertained during the medications development process.

Disulfiram has often been administered in the context of methadone maintenance to facilitate alcohol abstinence (Charuvastra et al., 1976; Ling, Weiss, Charuvastra, & O'Brien, 1983), having a long history as a treatment modality for alcohol dependence (Johnson, 2008). By inhibiting the enzyme *acetaldehyde dehydrogenase*, disulfiram increases the concentration of acetaldehyde in the blood following alcohol ingestion, prompting severe, unpleasant side effects that provide the basis of the aversion therapy model.

More recently, disulfiram has been studied as an agent for use in the treatment of cocaine dependence (K.M. Carroll et al., 2004; Oliveto et al., 2011; Petrakis et al., 2000). Although the initial rationale for using disulfiram was to decrease the high prevalence of concomitant alcohol use among cocaine users as an indirect method for reducing cocaine use (K. M. Carroll, Rounsaville, & Bryant, 1993), disulfiram appears to directly impact the actions of cocaine, enhancing the unpleasant effects of cocaine (Hameedi et al., 1995). The mechanism underlying this effect may be that disulfiram is also an inhibitor of the enzyme *dopamine β -hydroxylase*, which converts dopamine to norepinephrine (Goldstein, Anagnoste, Lauber, & McKereghan, 1964). Disulfiram thus increases basal dopamine: norepinephrine ratio, which is thought to modulate responses to cocaine (Schroeder et al., 2010). There is evidence to suggest that disulfiram at 250 mg/day reduces cocaine use in cocaine-dependent and/or dually-dependent cocaine- and opiate-dependent populations (K.M. Carroll, et al., 2004; Petrakis, et al., 2000).

While disulfiram itself is not considered an agent typically responsible for QTc prolongation, it is known to cause metabolic derangements (Johnson, 2008; Schroeder, et al., 2010) and has differential effects on cocaine and methadone metabolism. For instance, disulfiram increases cocaine plasma levels through inhibition of plasma esterases, which may result in cocaine accumulation and toxicity (Baker, Jatlow, & McCance-Katz, 2007). Conversely, disulfiram may increase the clearance of methadone (Tong, Benowitz, & Kreek, 1980), which may provide a protective effect against QTc prolongation. Thus, we

prospectively examined the impact of disulfiram on QTc interval in opioid- and non opioid-dependent cocaine dependent patients participating in an ongoing, 14 week, randomized, double blind, placebo-controlled clinical trial that included stabilization on methadone for those dependent on opioids. In addition, because cocaine use may be a complicating factor in our analysis, we included both recent cocaine use and methadone treatment status in our model.

METHODS

Opioid- and non opioid-dependent cocaine abusers who agreed to participate in an ongoing parent clinical trial examining the efficacy of disulfiram to treat cocaine dependence (Oliveto et al., 2012) were enrolled in these study procedures between August 2009 and September 2011. Each participant gave written informed consent, as approved by the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board. Participants (aged 18-65 years) were current cocaine users with at least weekly self-reported use during the month preceding study entry. Those presenting with a history of opioid dependence had either laboratory confirmation of opioid use during the month prior to study entry or manifested opioid withdrawal. Participants met DSM-IV criteria for cocaine dependence and, for chronic opioid users, opioid dependence. Exclusion criteria included current alcohol physical dependence, abnormal liver function (with laboratory enzyme levels greater than three times normal), active hepatitis, hypertension, a current cardiac condition, occult coronary artery disease, at least 3 risk factors for cardiovascular disease, seizure disorders, other significant medical condition contraindicating disulfiram and/or methadone treatment, history of schizophrenia, bipolar disorder, other psychotic disorders, current suicidality or homicidality, current use of a prescribed psychotropic medication that could not be discontinued, current use of medications such as anticoagulants, isoniazid, metronidazole, clotrimazole, and paraldehyde, benzodiazepine-positive urine toxicology screen, and, for women, pregnancy or breastfeeding.

In this 14-week, randomized, double blind clinical trial, opioid dependent (MT) participants were inducted onto methadone (wks 1-2) and both MT and untreated, nonopioid dependent (UT) participants were randomized to receive disulfiram (wks 3-14) at one of the following doses: 0, 250, 375, or 500 mg/day. The data manager performed the randomization based on opioid dependence status using a computerized urn randomization program (Wei & Lachin, 1988), balancing groups on age, sex, race and Cocaine Selective Severity Assessment score (Kampman et al., 1998). Only the research pharmacist and data manager were aware of the medication condition.

Participants attended clinic at the UAMS Substance Abuse Treatment Clinic three (UT participants) to six (MT participants) days/wk (M-S) to complete study tasks, undergo counseling and receive study medications. On Saturday, MT participants received study medications to take on Sunday. For MT participants, methadone dispensing procedures occurred as described previously (Oliveto, et al., 2011). Participants ingested methadone in a colored liquid daily at the dispensing window under observation of the dispensing nurse (except on Sundays, for which take home doses were provided). Participants initially received 25 mg of methadone. This dose was increased by 5 mg/day until participants received an initial maintenance dose of 60 mg/day (day 1 of week 2). The maintenance dose was adjusted as necessary thereafter, depending upon withdrawal symptoms or side effects. During weeks 3-14, either crushed disulfiram tablets or placebo (i.e., 300 mg of microcrystalline cellulose) was suspended in the methadone solution. Participants were advised to avoid alcohol or alcohol-containing products. At the beginning of week 15, disulfiram or placebo was no longer suspended in the methadone. At the end of the study,

participants either transferred to a local methadone program after a 2-week washout period or underwent detoxification from methadone over a 4-6 week period.

For UT participants, placebo (microcrystalline cellulose) capsules were prepared by the UAMS Research Pharmacy and disulfiram capsules were compounded by Cantrell Drug Pharmacy (Little Rock, AR) using disulfiram powder (Disulfiram USP) and microcrystalline cellulose. The UAMS Research Pharmacy packaged capsules into weekly blister packs. During week 3, participants attended clinic for 5 days and took the medication under staff supervision, receiving the rest of their blister pack to take doses during the weekend. Participants returned their blister packs each week (to conduct pill counts as a compliance measure) and receive the next weekly blisterpack, taking the first dose for any given week under staff observation. At the beginning of week 15, disulfiram or placebo was discontinued, and the participants were monitored for an additional 2 weeks thereafter to provide for adequate washout of the drug before discharge.

At intake, a demographics form, the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995), the Addiction Severity Index (McLellan, Luborsky, Woody, & O'Brien, 1980), and the Cocaine Selective Severity Assessment (CSSA) were completed. Supervised urine samples were obtained thrice weekly and tested for the presence of cocaine metabolite (benzoylecgonine) and other drugs using a Hitachi 717 Automated Analyzers (Boehringer Mannheim Corp., Indianapolis, IN), with a cut-off concentration of 300 ng/ml. Standard 12-lead electrocardiograms (ECGs) were performed during screening (week 0), week 2, and week 4 using a GE medical systems MA 1200 model ECG machine and the automated QTc result using Bazett's formula was recorded. ECGs were obtained by placing the participant in a supine position. After resting for three minutes, three ECGs were recorded 3 minutes apart. The primary variable of interest was median QTc interval.

MT and UT baseline characteristics were compared using a paired two-sample t-test for continuous variables and chi-square tests for dichotomous variables. Screening urine data (week 0), and urine data from weeks 2 and 4 were used to determine recent cocaine use typically on the day the ECG was performed or the day prior to obtaining the ECG. Median QTc interval data were entered into a repeated-measures, mixed model analysis of variance (ANOVA) with disulfiram dose (0, 250, 375, 500 mg/day), methadone treatment status (MT or UT), and recent cocaine use (yes or no) as between-subject factors and time (0, 2, 4 weeks) as the within-subject factor. Tukey's test was used to make multiple post-hoc comparisons and Dunnett's test to contrast placebo/cocaine negative urine results with disulfiram doses/positive cocaine urine results. The relationship between methadone dose and QTc interval was determined using Pearson R. Analyses were conducted using the Proc GLM procedure in SAS/STAT 9.3. A $p < 0.05$ was used to determine statistical significance and $0.1 > p > 0.05$ was used to determine a trend toward statistical significance.

RESULTS

Subject Characteristics

Seventy-three of 118 participants enrolled in the parent clinical trial (Oliveto, et al., 2012) participated in this protocol. Of these, 41 (23 MT; 18 UT) had complete data for our study. ECGs were not obtained at the appropriate time point in 32 subjects due to a holiday (N=2), staff error (N=4) or participant's leaving the protocol early (N=26). Reasons for early discharge include the following: voluntarily withdrawing consent as decided not to participate (N=1), had a conflicting work schedule (N=2) or went into a treatment facility (N=1); noncompliance with taking study medication (N=6); noncompliance with submitting urine samples (N=10); and noncompliance with other protocol requirements (N=3). The PI

terminated participation of two subjects due to suicidal ideation (N=1) and refusing to stop drinking alcohol (N=2). Noncompleters did not differ from completers in terms of baseline QTc interval (410.4 $\pm$ 13.5 versus 413.7 $\pm$ 16.4; $p=0.35$) or sex ($X^2=0.1$; $p=0.73$), but did differ by race ($X^2=9.0$; $p=0.003$). This difference was due to the large proportion of UT noncompleters who were mainly African American. Among UT participants, completers and noncompleters did not differ by race ($X^2=0.0$, $p=1.0$).

The MT and UT group differed with respect to race, in that the vast majority of the UT participants were African American whereas all MT participants were Caucasian (see table 1). Subject characteristics did not differ in regards to age, sex, education or self-reported number of days in the past 30 that participants used cocaine; however, UT participants reported significantly longer lifetime cocaine use (table 1). MT participants were receiving methadone at an average daily dose of 64.1 mg (range: 45-100) and 67.8 mg (range: 45-100) during weeks 2 and 4, respectively.

Impact of Disulfiram Dose, MT Status, and Time

No main effect of disulfiram dose for QTc interval was observed ($F=1.04$; $df=3$; $p=0.38$), with those in the placebo and disulfiram groups having mean QTc intervals of 414.1 $\pm$ 15.0 ms and 416.2 $\pm$ 19.2 ms, respectively. Moreover, QTc interval did not differ significantly in MT (418.3 $\pm$ 17.5 ms) relative to UT (412.0 $\pm$ 18.0 ms) participants, regardless of time ($F=1.15$; $df=1$; $p=0.29$, see figure 1, top panel). QTc interval showed no significant changes over time regardless of disulfiram dose or MT status ($F=0.48$; $df=1$; $p=0.62$). In addition no disulfiram dose X MT status interaction ($F=0.53$; $df=3$; $p=0.66$) nor any interaction with time (p values >0.42) was noted (data not shown).

For MT participants, no relationship between methadone dose and QTc interval was observed. Data obtained during week 2 and 4 had Pearson correlation coefficients of 0.04 and 0.09, respectively (data not shown). Similarly, no relationship between methadone dose and change in QTc interval from baseline was observed at either time point (data not shown).

Impact of Recent Cocaine Use

The proportion of urine samples positive for cocaine did not differ by disulfiram dose or MT status at any time point (p values >0.1 ; data not shown). The mean proportion of cocaine-positive urine samples positive for cocaine was significantly greater during screening relative to week 2 or 4, with 56.1%, 36.6% and 34.2% of urine samples positive for cocaine at week 0, 2, and 4, respectively ($X^2=4.01$, $p<0.05$).

Regardless of disulfiram dose, MT status or time, those with cocaine-positive urine samples immediately prior to the EKG exhibited significantly higher QTc intervals than those with cocaine-negative urine samples ($F=7.67$; $df=1$; $p=0.007$; see figure 2, bottom panel). There were no significant interactions with MT status ($F=0.74$; $df=1$; $p=0.39$) and/or time (p values > 0.42 ; data not shown).

There was a cocaine use X disulfiram dose interaction ($F=2.92$; $df=3$; $p=0.04$; see figure 2). QTc interval was significantly greater in the 250 disulfiram condition with recent cocaine use relative to all active disulfiram (250, 375, and 500) conditions without cocaine use. QTc interval was also significantly greater in the 250 disulfiram condition with recent cocaine use relative to the placebo condition with, but not without, cocaine use ($p<0.05$). Comparisons with the 375 disulfiram with cocaine use could not be made due to the small sample size of that group (i.e., N=1). Nevertheless, there were no interactions between cocaine use and time, including cocaine use X medcode X time interaction ($p>0.40$).

Two MT and one UT individuals had at least one median QTc interval greater than normal, defined as 450 msec for males and 470 msec for females (Martell, et al., 2005). One MT male had a QTc reading of 460 msec at week 0 and 453 msec at week 2 along with cocaine positive urine samples; the QTc interval was within the normal range at week 4. Another MT male had a QTc interval reading of 452 msec at week 2 with a cocaine-negative urine sample, but the others were within normal limits. One UT male showed a QTc interval of 478 msec during week 2, along with a cocaine-positive urine. No female participant presented with a QTc interval greater than 470 msec at any time point.

DISCUSSION

Our findings suggest that disulfiram at doses of 250-500 mg/day appears to have no effect on QTc interval, whether or not MT status and/or time is taken into account. In addition, the only instances of QTc prolongation beyond the normal range occurred prior to beginning disulfiram administration. To our knowledge, this is the first time that the effect of disulfiram on QTc interval has been studied in these populations. Although we showed a disulfiram dose by cocaine use interaction, these findings were irrespective of time. Thus, given that disulfiram was being administered only during the 4-week assessment, these findings are likely more indicative of a potential sampling bias than a direct effect of disulfiram. These findings are consistent with prior work suggesting that disulfiram increases methadone clearance (Tong, et al., 1980) and suggest that disulfiram has a good safety profile in terms of QTc effects, regardless of MT status.

Although not the overarching aim of the study, one strength of this study is that changes in QTc interval in MT individuals could be examined relative to a UT control under controlled conditions. Our findings seem to suggest that there were no differences in QTc interval based on MT status or MT status and time, which is inconsistent with prior reports that methadone-maintained individuals have significantly prolonged QTc intervals relative to baseline (Fareed et al., 2010; Martell, et al., 2005). However, the sample size of the present study was very small relative to other studies and so likely underpowered to detect differences, particularly given that the mean QTc interval appeared higher in the MT group relative to UT controls. For instance, one study from Copenhagen examined the effects of large doses of methadone on the QTc interval in 450 patients enrolled in a methadone maintenance clinic (Fanoe, Hvidt, Ege, & Jensen, 2007). One more recent cross-sectional study shows the effects of smaller doses of methadone on QTc in a sample of 283 patients overall (Chang et al., 2012). Indeed, Maremmani and colleagues (Maremmani et al., 2005) showed that 83% of 83 methadone patients had longer QTc intervals relative to age- and sex-matched reference values.

Other methodological differences may also account for this inconsistency. For instance, all MT participants in the present study abused prescription opioid analgesics rather than heroin, which was the drug of choice among participants in prior studies (Fanoe, et al., 2007) and is noted for its relatively short half-life (Sawynok, 1986). Thus, QTc prolongation may be less of an issue in individuals dependent on longer-acting opioids who are placed on methadone maintenance. A recent report in advanced cancer patients showed no clinically significant increase, if any, in QTc interval after switching to methadone maintenance from another opioid analgesic; however, the sample size was also quite low in this study (Reddy et al., 2010). Moreover, similar to this prior study (Reddy, et al., 2010), our QTc assessments occurred only a few weeks apart, rather than months apart, as in other reports (Fareed, et al., 2010; Martell, et al., 2005). Methadone maintenance doses also ranged from 45-100 mg/day in the present study, which is lower than that reported in studies showing a significant association between methadone dose and QTc prolongation (Fareed, et al., 2010; Krantz, et al., 2005). Thus, methadone levels likely did not achieve steady state by the end

of week 2, although they should have by week 4. In addition, unlike previous samples (Fanoë, et al., 2007; Fareed, et al., 2010; Krantz, et al., 2005; Martell, et al., 2005; Reddy, et al., 2010), our sample consisted of individuals specifically with cocaine dependence. These methodological issues may account, at least in part, for the difference in findings.

Importantly, recent cocaine use was associated with significantly greater QTc intervals, regardless of MT status. This finding is consistent with previous reports (Fareed, et al., 2010; Levin, et al., 2008; Magnano, et al., 2006). Cocaine administration to humans under controlled laboratory conditions has been shown to transiently prolong QTc interval (Magnano, et al., 2006). Moreover, QTc interval was shown to decrease in habitual cocaine users who abruptly underwent a period of monitored cocaine abstinence (Levin, et al., 2008). One study in methadone-maintained patients found that cocaine-positive urine samples were associated with prolonged QTc (Fareed, et al., 2010). The present findings extend these results by showing that cocaine use is a risk factor for QTc prolongation in both MT and UT cocaine-dependent individuals.

Strengths of the study include the prospective design, inclusion of a UT control, testing multiple doses of disulfiram, and a rigorous double blind, placebo-controlled clinical trial methodology. The limitations of this study include that the sample size was relatively small, which didn't allow for many multiple comparisons and may be preventing detection of statistically significant changes in QTc between the MT and UT groups. Moreover, it is unclear how racial differences between MT and UT participants may have impacted QTc interval. In addition, the QTc interval was not manually calculated, but recorded from the ECG readout, although automated results have been shown to be more accurate in healthy individuals (Kautzner, 2002). Finally, we recognize that these results may not be easily generalizable to the general cocaine dependent population because of the study's strict exclusion criteria.

CONCLUSIONS

Disulfiram is an old drug that may be finding a new purpose as a possible treatment modality for cocaine dependence, both in cocaine-dependent and dually cocaine- and opiate-dependent populations. Our study suggests that disulfiram may not prolong QTc interval. Moreover, our findings suggest that cocaine use may be a highly salient factor to consider when assessing drug-induced QTc alterations in both MT and UT populations. More work is needed in larger populations to clarify the relative impact of these and other factors on QTc.

Acknowledgments

This work was supported by grants R01 DA013441 and T32 DA022981 (TA, NS) from the National Institute on Drug Abuse and 1UL1RR029884 (MJM, AO) from the National Center for Research Resources. This work was also supported by the UAMS College of Medicine Honors in Research Program (TA). The authors thank Jeff Thostenson for his assistance with a few of the data analyses and Summer Alexander for her assistance with manuscript preparation.

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Figure 1.

The impact of MT status (top panel) as well as recent cocaine use (bottom panel) on QTc interval: MT (closed circles), UT (open circles); recent cocaine use (COC+, closed circles) and no recent cocaine use (COC-, open circles). Each point represents the mean $\pm$ SD.

Figure 2.

The impact of disulfiram dose (0, 250, 375, 500 mg/day) and recent cocaine use on QTc interval: Cocaine-negative urines (COC-, gray bars), cocaine-positive urines (COC+, black bars). Each bar represents the mean $\pm$ SD.

Table 1

Participant Characteristics.

Measure	MT (N=23)	UT (N=18)	Statistic	P Value
Sex (% Female)	52.2	27.8	Chi2=2.48	0.12
Race (Cauc/AA/Latino)	23/0/0	2/14/1	Chi2=33.53	<0.001
Age (mean (SD))	40.1 (13.1)	46.4 (6.2)	t=1.906	0.064
Education (<HS grad/ HS grad)	5/18	9/9	Chi2=3.59	0.058
<i>SCID Diagnoses (%)</i> :				
Cocaine Dependence (%)	100	100	--	--
Opioid Dependence (%)	100	0	--	--
<i>Self-Reported Cocaine Use (mean(SD))</i> :				
Cocaine Use (# days in last month)	11.04 (.73)	12.83 (9.07)	rank sum test	0.53
Cocaine Use (# years of use)	7.17 (7.22)	12.89 (11.5)	rank sum test	0.01

MT, methadone treated

UT, untreated (non opioid-dependent)

SCID, Structured Clinical Interview for DSM-IV