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The Presence or Absence of QTc Prolongation in Buprenorphine-Naloxone Among Youth with Opioid Dependence

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Abstract

Objective—To evaluate buprenorphine-naloxone effects on the QTc in youth with opioid dependence. Buprenorphine is a partial agonist that is an effective treatment for opioid dependence. Compared to methadone it has a lower risk of QTc prolongation in adults but is less well studied in youth. It may also reduce the risk for torsades de pointes (TdP) an uncommon variant of polymorphic ventricular tachycardia, that can result in syncope, ventricular fibrillation, and sudden death.

Methods—Secondary analysis of ECG data from 95 subjects who participated in a multi-site trial for youth with opioid dependence. Subjects were randomized to a 2-week (DETOX), or a 12-week course of buprenorphine-naloxone (BUP). 12-lead ECGs were done at baseline, weeks 4 and 12, and QTc intervals were hand measured and calculated using Bazett's formula. Increases > 60 milliseconds (ms) were considered clinically significant, and readings > 450 ms (males) and 470 ms (females) indicated a prolonged QTc.

Results—Mean QTc intervals were higher for BUP than DETOX participants at baseline, week 4, and week 12 ($p = 0.045$), and females had longer mean QTc intervals than males ($p < 0.0005$). Variations in QTc intervals were observed in some, however none were above 500 ms, the level at which risk for TdP becomes more significant.

Conclusion—In this randomized trial, the mean QTc at baseline, before randomization, was higher in BUP than DETOX patients. Minimal changes in the QTc were seen at 4 and 12-weeks in a few patients in both groups. There was no evidence that buprenorphine-naloxone alone increased the QTc to a level that increased the risk for TdP.

Keywords

QTc interval; young adults; Buprenorphine-naloxone; Suboxone®

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Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of the National Institute on Drug Abuse or the Center for Clinical Trials Network. Drs. Poole and Woody had access to all study data and take full responsibility its integrity and the accuracy of the analyses.

The QT interval is the duration of electrical activation and recovery of the ventricular muscle between the onset of ventricular depolarization as it contracts and the end of repolarization as it relaxes, and is measured from the onset of the Q wave to the end of the T wave on the electrocardiogram (ECG). Since this duration can vary inversely with heart rate, it is typically corrected using the Bazett formula (Bazett, 1997; Hosmane, Locke, & Morris, 2006) and reported as the corrected QT interval (QTc). Prolongation of the QTc increases the risk for torsades de pointes (TdP), a ventricular arrhythmia that can result in syncope, ventricular fibrillation, and sudden death (Beach, Celano, Noseworthy, Januzzi, & Huffman, 2013; Krantz, Lewkowicz, Hays, Woodroffe, Robertson, & Mehler, 2002; Sticherling, Schaer, Ammann, Maeder, & Osswald, 2005). The diagnosis of borderline prolongation has been typically given when QTc values are between 440 and 470 ms (Moss, 1993; Levine, Rosero, & Budzikowski et al., 2008); however, data from several studies have associated significant risk for TdP at levels at or above 500 ms (Priori, Swartz & Napolitano et al., 2003; Sauer, Moss & McNitt et al. 2007; Salvi, Karnad, Panicker et al., 2011; Malik, 2001; Levine, Rosero, & Budzikowski et al.; Moss, 1993; Krantz, Martin, Stimmel, Mehta, & Haigney, 2009).

Prior research has shown that methadone, an opiate agonist used in the treatment of chronic pain and opiate use disorders, can prolong the QTc (Jayasinghe, & Kovoov, 2002; van Noord, Eijgelsheim, & Stricker, 2010) and has led some to recommend that ECGs be done prior to starting methadone maintenance with a follow-up several months to a year later (Maremmanni, Pacini, Claudio, Perugi et al., 2005; Wernicke, Faries, Breitung, & Girod, 2005); others have criticized this recommendation as overly conservative (Pani, Trogu, Maremani & Pacini, 2013; Anchersen, Clausen, Gossop, Hansteen, & Waal, 2009). Buprenorphine, a Schedule III opioid partial agonist used in the U.S. in a sublingual preparation containing four parts buprenorphine to one part naloxone (Suboxone®), or in newer formulations (Zubsolv®; Bunaval®) with similar but not identical proportions of buprenorphine to naloxone, appears to have less risk for QT prolongation than methadone (Downing, Leary, & White, 1977; Baker, Best, Pade, McCance-Katz, 2006; Johnson, Chutuape, Strain, Walsh, Stitzer, & Bigelow, 2000; Krantz, Garcia, & Mehler 2005). In a study by Anchersen et al. (2009), 29% of 173 adults that were treated with methadone had a QTc > 450 ms with 15% > 470 ms, but none of the 27 buprenorphine patients had QTc > 450 ms. A similar finding was seen by Wedam et al. among 154 adults in a 17-week, randomized, double-blind trial of methadone, levo-alpha-acetyl methadol (LAAM), and buprenorphine (Wedam, Bigelow, & Johnson, 2007). Findings showed a significant increase in mean QTc in the LAAM [27 (±4.8) ms], and methadone groups [17.03 (±5.0) ms] but not in the buprenorphine group [5.4 (±4.1) ms]. While there is no reason to think that findings would be different in opioid dependent youth being treated with buprenorphine-naloxone, few data are available on this younger group. Here we present QTc data from a secondary analysis of ECG findings from a study using buprenorphine-naloxone for treatment in these patients.

METHODS

Study Overview

Youth with opioid dependence aged 15–21 years, seeking outpatient treatment were randomized to either: 1) brief stabilization on buprenorphine-naloxone followed by a dose taper to zero that ended by day 14 (DETOX); or, 2) short-term buprenorphine-naloxone maintenance with a dose taper beginning in week 10 and completed by the end of week 12 (BUP). All participants received weekly drug counseling and urine drug screens with more detailed assessments at weeks 4, 8, and 12. Doses of buprenorphine/naloxone were flexible, based on clinical assessments, and administered under direct observation except when take-homes were given at sites that were closed on weekends. The primary outcome was opioid positive urine tests at weeks 4, 8, and 12 and the results showed significantly better outcomes in BUP on the primary and secondary outcomes as compared to DETOX (Woody et al, 2008). ECGs were done at baseline, week 4, and week 12 as part of a safety assessment, thus providing data on the impact of buprenorphine-naloxone on the QTc interval in this younger population.

Setting and Participants

Six addiction treatment programs participated in the study: Brandywine Counseling, Newark, DE; Mountain Manor Treatment Center, Baltimore, MD; Duke Addictions Program, Durham, NC; Ayundantes Inc., Española, NM; University of New Mexico Addiction and Substance Abuse Programs, Albuquerque, NM; and Mercy Recovery, Westbrook, ME. The study was approved by the institutional review board at the University of Pennsylvania and by IRBs at all participating sites.

Inclusion criteria for the original study included subjects 15–21 years of age; seeking outpatient treatment for opioid dependence with physiologic features according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition -Text Revision (DSM-IV-TR); absence of serious medical or psychiatric disorders that might impair or make hazardous their ability to provide informed consent or participate; and ability to give subject assent and parental consent for individuals aged 15–17. Exclusion criteria included abusing alcohol or sedatives for 15 or more days in the last 30; inability to provide a urine test negative for benzodiazepines and methadone (3 tries permitted); plans to move from the immediate area or to be incarcerated in the near future; currently receiving other addiction treatment; a baseline ECG showing a PR interval or QRS that was abnormal for the patient's age or a QTc > 450 ms for males or > 470 ms for females. Additional details about inclusion criteria and secondary outcomes are described in the primary outcome paper (Woody et al, 2008). Though 152 participants were randomized, the analyses represented here focused on the 95 subjects who had follow-up ECGs; 70 who had ECGs at weeks 4 and 12 (31 DETOX; 39 BUP) and 25 who had ECGs at week 4, but not week 12 (12 DETOX; 13 BUP).

Dosing

Buprenorphine-naloxone dosing followed the clinical guidelines of not > 32 mgs/day and was adjusted according to clinical response. The mean dose at week 4 for BUP participants was 14.3 (± 6.2) mgs ($n = 52$); at week 12 it was 2.3 (± 3.5 ; $N=39$). Although DETOX

participants were tapered from study medication by week 2, some (N=17) reported use of buprenorphine-naloxone outside the study resulting in a self-reported mean dose of 3.2 (± 4.4) mgs for the entire DETOX group at week 4 and 4.4 mgs (± 4.8) at week 12 (N=31).

ECG Assessments

The ECGs were acquired in a supine position, according to a standard protocol on Schiller AT21 Interpretive ECG machines. The waveforms were digitally acquired with an analog copy printed on paper. A PDF of the paper ECG was emailed to the pediatric cardiologist (VLV) who was blinded to the patient's treatment examined all ECGs to determine if they exceeded the study admission threshold of 450 ms for males or 470 ms for females. QT intervals were hand measured and corrected for heart rate using Bazett's formula ($QTc = QT / RR$) to obtain QTc values independent of underlying heart rate. No corrections were made for rates less than 60 bpm.

Data Management and Statistical Analysis

Data were analyzed according to treatment assignment and included possible correlates of QTc prolongation such as dose level, duration of buprenorphine-naloxone, alcohol use, and concurrent drug use (mainly psychotropic medications). Alcohol was included as several studies reported that prolonged QTc has been associated with binge drinking in men (Zhang, Post & Dalal et al., 2011); and with acute alcohol withdrawal in both genders (Otero-Anton, Gonzalez-Quintella & Saborido et al., 1997). Between-group and within subjects measures compared baseline to week 4 QTc intervals using an analysis of variance according to IBM SPSS version 19 (Armonk, New York) and SAS 9.2 (SAS, Inc., Cary, North Carolina). Analyses were stratified by treatment, with and without sex, and dose using 95% CI at $p < 0.05$. We also did a separate analysis looking for site differences. Sample size calculation aimed at detecting a QTc change difference in the two groups had a power of 0.80 and an effect size of 0.28, critical $F=3.93$. A Cox regression analysis was performed on dose and QTc to examine risk factors and regression coefficients for prolongation of the QTc, and a survival analysis determined if QTc changes were associated with study dropout.

RESULTS

All ECGs were within normal limits at baseline as per study admission criteria and there were no differences in age, sex, lifetime drug use or other demographic features between groups except for one 15 year-old in the BUP group (Table 1). Baseline and week 4 ECGs were available for 95 participants but 25 of these missed their 12-week evaluation, thus only 70 ECGs were available on these 95 at all three measurements.

QTc means by treatment (Figure 1) showed a significant baseline difference between conditions ($p = 0.045$) but no time effect (baseline = 409.7 [± 20.4] for BUP/N = 52; 399.9 [± 21.4] for DETOX/N = 43; week 4 = 410.8 [± 25.9] for BUP/N = 52; 405.9 [± 23.4] for DETOX/N = 43; week 12 = 410.7 [± 28.3] for BUP/N = 39; 406.8 [± 28.2] for DETOX/N=31). A test of fixed effects by site found that treatment and sex were significant between groups but there was no site effect ($df=5$, $F=1.251$, $p=.286$, $n=95$) and no site by dose effect ($p=.387$). At the individual level, no females had a QTc greater than 470 ms for any

measurement however three males - one DETOX and two BUP - exceeded the 450 ms threshold after baseline. The DETOX male had a baseline and week 4 QTc of 380 ms that increased to 470 ms by week 12 (+90 ms). He completed a dose taper at week 2 but was prescribed 25 mg of paroxetine between week 4 and 12, a medication known to increase the QTc. Of the two BUP males, one had a QTc of 400 ms at baseline that increased to 410 at week 4 and to 450 ms at week 12; he was prescribed paroxetine at week 4. The second male had a QTc of 420 ms at baseline that decreased to 410 ms at week 4 and increased to 462 ms at week 12; he was prescribed 300 mg trazodone per day at baseline and received methocarbamol and hydroxyzine during the first 4 study weeks. Trazodone was discontinued after week 4 and he received only methocarbamol and hydroxyzine between weeks 4 and 12, however his urine was positive for opiates, oxycodone, and cannabinoids at week 12. Three other males had QTc increases of > 60 ms that did not reach 450 ms; two were in DETOX and one in BUP. Of the two in DETOX, one had a QTc of 330 ms at baseline that increased to 400 ms at week 4; he had received olanzapine, also known to prolong the QTc, but dropped out before week 12. The second DETOX male increased his QTc from 360 ms at baseline to 440 ms at week 4 then decreased to 375 ms by week 12; he was prescribed methocarbamol prior to week 4. The BUP male had a QTc of 390 ms at baseline that decreased to 340 ms at week 4 and increased to 400 ms at week 12; he was prescribed clonidine at week 4.

Gender Effects

As expected, the mean QTc for females was higher than for males ($p < 0.0005$), regardless of treatment condition (Figure 2). QTc changes among BUP males between baseline and week 4 ($N = 27$) ranged from -33 to +58 ms (mean +2.19 [± 23.1]), and from -37 to +52 (mean +2.1 [± 25.1]) between week 4 and week 12 ($N = 18$). Change in QTc from baseline to week 4 in BUP females ($N=25$) ranged from -50 to 39 ms (Mean = -1.4 [± 21.9]) and -32 to 60 ms (mean = +3 [± 21.5]) from week 4 to week 12 ($N = 21$). A regression analysis by dose and gender showed an upward trend for men and women when groups were combined.

Cox regression showed the risk for QTc prolongation by treatment was not significant ($p=0.143$, $n=95$). Risk of prolongation also did not vary as a function of gender (hazard ratio = .51, 95% CI = .21–1.23; $p = .14$) or dose (hazard ratio = 1.02, 95% CI = .93–1.11; $p = .73$). The lack of relationship between dose and prolongation risk was not surprising given that in most cases dose had been tapered by the second time period for the Detox group and tapering for both groups by week 12

Non-Study Dosing

The dose of non-study buprenorphine-naloxone could not be independently verified for patients receiving treatment outside the clinics, therefore DETOX patients that reported having received buprenorphine-naloxone at the end of their dose taper in week 2 were analyzed both separately and within their original group assignment. We termed this group DETOXPLUS. Results showed that the mean dose for DETOXPLUS, was 7.3 (± 3.2) mgs ($n = 17$) at week 4, and 8.0 (± 3.0) mgs at week 12 ($n = 16$). Baseline to week 4 and baseline to week 12 comparisons of the mean QTc for the DETOX, BUP, and DETOXPLUS groups

showed no differences by treatment group and no subjects had QTc prolongations >60 ms or were above 450 ms for males or 470 ms for females.

Prescribed Psychotropic Medication and Other Drug Use

Seventeen of the 95 participants who had baseline and week 4 ECGs began the study on prescribed psychotropic medication. Thirteen were on antidepressants (citalopram, escitalopram and/or trazodone) and 4 were on antipsychotics (quetiapine or promethazine). Medications were discontinued on four by week 4.

At week 12, an analysis of variance showed a significant difference between 6 participants (4 females and 2 males) who were on antidepressants at baseline and at week 12 ($427.5 [\pm 24.9]$) as compared to those that were not on psychotropic medication ($400.1 [\pm 27.1]$, $p = 0.024$). All six were BUP patients, some on multiple medications that included trazodone ($n=4$), escitalopram ($n = 2$), paroxetine ($n = 1$), sertraline ($n = 2$), and venlafaxine ($n = 1$). Paroxetine, sertraline, escitalopram and venlafaxine are known to prolong the QTc (22). Three of the 6 were prescribed trazodone at baseline and then switched to fluoxetine or sertraline or had paroxetine added to their trazodone by week 12. Two others were given escitalopram at baseline and continued on it through week 12; one was on sertraline throughout the study. None of the 6 had increases over 60 ms, however a BUP male who received paroxetine and trazodone throughout the study had a QTc of 450 at week 12, up 40 ms from week 4. None of the four BUP females had a QTc greater than 470 ms at weeks 4 or week 12.

Two multiple regression analyses were performed on the 95 subjects that had follow-up ECGs looking for possible predictors of QTc increases associated with illicit drug use. In the first model (Table 2) we entered the three time points, week 0, week 4, and week 12, sex, and treatment condition. Time was used as a categorical variable, and therefore coded into a dichotomous dummy variable and entered with sex and treatment. The results were similar to other findings in which treatment and sex were found to have a significant relationship to QTc levels, but time did not. We did not use hierarchical loading of the variables into the model, but loaded all variables using the direct entry method. The results showed that sex and treatment explained a significant amount of the variance ($F [4,255] = 12.444$, $p < .05$, $R^2 = .40$, R^2 adjusted = .15); sex (Beta = .375, $t (259) = 6.545$, $p < .000$); treatment (Beta = .129, $t (259) = 2.249$, $p < .05$, $n = 95$).

In the second multiple regression analysis we entered treatment, sex, alcohol, heroin, amphetamines, barbiturates, benzodiazepines, other sedatives, methadone, (illicit and prescribed), other opiates, tricyclic antidepressants, cocaine, methamphetamine, cannabinoids, nicotine, oxycodone, morphine, other hallucinogens, inhalants, and phencyclidine. Each substance was considered separately when loaded into the model, but was combined with treatment and sex. Again treatment and sex were always significant in each model and results showed that only prescribed methadone was a possible predictor of QTc values ($F [3, 256] = 19.077$, $p < .05$, $R^2 = .427$, R^2 adjusted = .17, $n = 95$). Since we could not tell whether it was males or females who were responsible for the significance we examined the descriptive statistics for methadone use by treatment and gender. The results

showed that females in the detox group had higher methadone use across the 12 weeks of the study than females in the BUP group or males in the DETOX and BUP groups.

All available ECG's were measured for Qtc. In an analysis of subjects with at least one ECG versus subjects with no ECGs, we compared baseline features to determine if there were any differences between subjects who did and did not have a follow-up ECG. The results showed that heroin use in the 30 days prior to study entry, lifetime sedative use, lifetime cocaine use, lifetime hallucinogen use, past 30 days use of hallucinogens, and past 30-day and lifetime inhalant use were more common in subjects that did not have a follow-up ECG.

We compared subjects who had week 12 ECGs to subjects without week 12 ECGs. Results of a univariate analysis showed no significant association between having a 12-week ECG except that lifetime hallucinogen use and longer periods of inhalant use were more likely to drop out of the study versus subjects with little or no hallucinogen or inhalant use ($df=1$, $F=6.570$, $p=.011$).

DISCUSSION

We found no clear evidence that short-term buprenorphine-naloxone treatment prolonged the QTc to 500 ms, the level that significantly increases the risk for TdP. The largest QTc increases were in patients prescribed psychotropic medications that are known to increase the QTc; the longer-term effect of buprenorphine-naloxone when co-prescribed with psychotropic medications could not be determined. While we know of no literature on ECG effects among adolescents using buprenorphine-naloxone with psychotropic medications, the effect of antipsychotic use alone was reported in a 6-month trial of 38 children and adolescents (mean age 15.1 years) who were prescribed second-generation antipsychotics and compared to 14 age-matched controls. The results showed that no patient had a QTc greater than 450 ms, and that the baseline QTc was unrelated to the QTc at month 6 ($p=0.072$). The mean change in QTc at 6 month was 6.34 (± 25.51) ms. The QTc at baseline was inversely related to QTc change ($p=0.001$); and antipsychotic drug use, sex, age, smoking status, substance abuse, and medical diagnoses were unrelated to QTc change (de Castro, Fraguas, Laita, Moreno, Parellada, & Pascual et al., 2008).

Participants were given urine toxicology screens for illicit drug use during the study as part of regular study procedures and many were found positive for other opiates, cocaine, marijuana and other substances. Analysis of illicit drug use between baseline and week 12 showed that only methadone appeared to have an association with QTc elevation and that was in DETOX females. The analysis also found that baseline screening for illicit drug use among both DETOX and BUP groups showed an association between multiple drug use prior to study entry, drop out, and missing week 12 data. These results suggest that females, who are known to have longer QTc intervals than males and who also tested positive for methadone more often than males in both groups, may have accounted for some of these differences.

Another study reviewed the medical records of 811 psychiatric inpatients (mean age 15.5 (± 2.4)) that were on antipsychotics and found that 16 had QTc > 440 ms (range: 442 – 481

ms; mean 454 ms, 1.97%; 95% CI: 1.17% – 3.25%). In a 1:5 nested case–control design, the 16 patients with QTc > 440 ms were matched with 80 patients with QTc < 421 ms. While both groups had similar proportions of antipsychotic use (43.8% vs. 40.8%), the results showed that hypokalemia ($p = 0.009$) and obesity ($p = 0.032$) were more common among patients with a prolonged QTc, and a significant correlation was observed between obesity and QTc prolongation (Correll, Harris, Figen, Kane, & Manu, 2011).

Limitations of the data presented here include the small sample sizes and the impact of current or past medical problems, exercise or other pharmacotherapies. The QTc was not measured at peak serum levels, the effect of naloxone could not be independently assessed, and the week 4 and 12 ECGs in the DETOX group represented a time when the patients were not on buprenorphine unless they received non-study medication (the DETOXPLUS group) and thus more like a control than a comparator group. We did not measure withdrawal symptoms and thus had no way of evaluating the potential impact of opioid withdrawal on the ECG nor could we evaluate the impact of current or past medical problems or pharmacotherapies, or buprenorphine-naloxone when administered over longer periods of time.

CONCLUSION

In summary this secondary analysis found no evidence that short-term buprenorphine-naloxone exposure significantly prolongs the QTc in opioid dependent youth. The results add to the known safety data on buprenorphine-naloxone among adults, and could add to the literature that buprenorphine-naloxone is a safe and effective treatment for opioid dependent young adults with clinically significant QTc prolongations or who are at risk for developing it if the results are replicated in other samples over a longer period of time. The few QTc prolongations that occurred were among participants who were receiving psychotropic medications that are known to prolong the QTc, and indicate a need for further evaluation of potential interactions between buprenorphine-naloxone and SSRI's or other commonly used psychotropic medications (Jolly, Gammage, Cheng, Bradburn, Banting, & Langman, 2009; Gil, Sala, Anguera, Chapinal, Cervantes, & Guma et al. 2003).

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Mean QTc for Figure 1

	DETOX /std	std error	(CI 95%)	BUP*/std	std error	(CI 95%)
Baseline	399.9 (±21.40)	3.73	(392.54-407.23)	409.7 (±20.41)	3.40	(403.03-416.39)
Week 4	405.9 (±23.40)	3.73	(398.56-413.26)	410.8 (±25.90)	3.40	(404.07-417.43)
Week 12	406.8 (±28.20)	4.40	(398.12-415.43)	410.7 (±28.30)	3.91	(403.00-418.43)

*P=0.045 treatment effect at .05

Figure 1.

Mean QTc at Baseline, Week 4, and Week 12 by Treatment

*P=0.045 treatment effect at .05

*P=0.036 treatment (sig=p>.05)

**P<0.000 sex (sig=p>.05)

Figure 2.

Mean QTc by Treatment and Gender Including Participants on Non-study Bup/Nal

*P=0.036 treatment (sig=p>.05)

**P<0.000 sex (sig=p>.05)

Table 1

Baseline Characteristics of Study Participants

Characteristics	Detox (N=43)	BUP-Nx (N=52)
Males	25 (58.1%)	29 (55.8%)
Females	18 (41.9%)	23 (44.2%)
Race	White	41 (78.8%)
	Hispanic	10 (19.2%)
Mean Age	Mean(N=43)	Mean(N=52)
	19.0	19.3
Mean Yrs Use Heroin Use	1.6 (72.1%)	1.5 (63.5%)
Mean Yrs Use Alcohol Use	1.0 (37.2%)	1.4 (42.3%)
Mean Yrs Prescription methadone Use	0.1 (7%)	0.1 (5.7%)
Mean Yrs illicit methadone Use	0.1 (7%)	0.1 (7.6%)
Mean Yrs Use Other Opiates	1.6 (60.5%)	1.7 (63.5%)
Mean Yrs Use Cocaine	0.7 (30.2%)	0.4 (77.0%)
Mean Yrs Use Marijuana	4.4 (93.0%)	3.5 (77.0%)
Mean Yrs Smoking	4.1 (88.4%)	4.6 (92.3%)
Mean Yrs Education	11.4	11.2
Percent Patients on antidepressants	11 (25.6%)	16 (30.8%)
Percent Patients on antipsychotics	5 (11.6%)	3 (5.8%)
Percent Patients on methadone	1 (2.3%)	0 (0)
Never Married	37 (86.0%)	48 (92.3%)
Worked Past 6 Months	18–30 y/o	34 (65.4%)
	11–18 y/o	3 (6.0%)
In School Past 6 Months	18–30 y/o	12 (23.1%)
Not in School currently	11–18 y/o	7 (13.4%)

Table 2**Summary of Other Drug Use**

Predictors of QTc For Other Illicit Drugs By Treatment and Gender (n= 95)						
Predictor Variables	B	SE	R sq	df	Beta	*Sig.
Time						
Model			.163	4	12.444	.000
Treatment	6.338	2.818			.129	.023
Sex	18.506	2.828			.375	.000
Baseline	-3.728	3.562			-.073	ns
Week 4	-.555	3.563			-.011	ns
Methadone						
Model			.183	3	19.077	.000
Treatment	7.598	2.816			.154	.007
Sex	18.324	2.788			.372	.000
Methadone	17.017	6.210			.157	.007

* Sig. p<.05

Table 3
Baseline Comparisons for Subjects with QTc versus Subjects without QTc (from original Study) N=152

Variables	N	Mean/%	Std	Std err	df	F	Sig.
<u>Sex</u>							
No QTc	31	(20.4%)			1	1.549	ns
	Males						
	Females	(9.9%)					
Yes QTc	60	(39.5%)					
	Males						
	Females	(30.3%)					
<u>Heroin/Days Past 30</u>							
No QTc	46	23.17	12.246	1.806	1	5.559	.020*
Yes QTc	105	17.81	13.128	.300			
<u>Heroin/Lifetime</u>							
No QTc	46	1.85	1.751	.258	1	1.247	ns
Yes QTc	105	1.53	1.520	.148			
<u>Other Opiates/Past 30 Days</u>							
No QTc	46	7.41	12.152	1.792	1	1.979	ns
Yes QTc	105	10.49	12.439	1.214			
<u>Other Opiates/Years</u>							
No QTc	46	1.11	1.792	.264	1	2.423	ns
Yes QTc	105	1.61	1.832	.179			
<u>Other Opiates/Rte of Administration</u>							
No QTc	46	4.76	3.212	.474	1	4.619	.033*
Yes QTc	105	3.63	2.873	.280			
<u>Sedatives/Lifetime</u>							
No QTc	46	.63	1.768	.261	1	4.974	.027*
Yes QTc	105	.20	.595	.058			
<u>Cocaine/Lifetime</u>							
No QTc	46	1.09	1.987	.293	1	4.058	
Yes QTc	105	.55	1.232	.120			.046*

Variables	N	Mean	Std	Std err	df	F	Sig.
<u>Hallucinogens/Lifetime</u>							
No QTc	46	.76	1.897	.283	1	4.600	.034*
Yes QTc	105	.29	.793	.077			
<u>Hallucinogens/Days Past 30</u>							
No QTc	46	.35	1.286	.190	1	4.195	.042*
Yes QTc	105	.08	.300	.029			
<u>Inhalants/Days Past 30</u>							
No QTc	46	.30	1.253	.186	1	5.696	.018*
Yes QTc	105	.01	.098	.010			
<u>Inhalants/Lifetime</u>							
No QTc	46	.39	1.653	.244	1	4.148	
Yes QTc	105	.05	.350	.034			.043*

* Significant at $P < .05$