

## Frequency of prolonged QT intervals in patients treated with methadone referred to an addiction treatment clinic in the north of Iran

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### Abstract

**Background and objective:** Despite the benefits of methadone and its widespread use in opioid treatment programs, this drug has various adverse side effects even at therapeutic doses. This study aimed to determine the frequency of long QT intervals in patients treated with methadone with doses lower than 100 mg.

**Materials and methods:** In this cross-sectional study, all the patients between 30-65 years of age admitted for methadone maintenance treatment were enrolled. A matched group of patients with no history of using methadone was included. Screening electrocardiography was performed for all participants at the beginning. Demographic data, drug history, QT interval, and Maximum QTc time were evaluated. The mean QT interval was compared with the defined normal value using the one sample t-test. Also, the mean QT interval based on the methadone dose consumption and other variables was analyzed using t-test or ANOVA statistical tests. *P*-value less than 0.05 was considered significant. The statistical analysis was performed using SPSS version 18.

**Results and conclusion:** Out of 196 subjects, 97 patients were in the methadone group. 83.5% of methadone users and 68.7% of the control group were males. The mean age was 43.8, and 44.5 in the methadone and control group, respectively. 83.5% of methadone users and 68.7% of the control group were males. In the methadone group, 17.5% had abnormal QTc-Max, while only 2% of the control group had abnormal QTc-Max (*P*=0.0001). Of the people who consumed less than 40 mg of methadone daily, 3.7%, and those who consumed more than 40 mg, 34.9% experienced abnormal QTc-Max (*P*=0.0001). This survey revealed that methadone use in even doses lower than 100 mg could also increase the risk of QT prolongation. Therefore, the treatment team needs to be aware that arrhythmias might occur within a wide range of methadone treatment doses.

**Keywords:** Dysrhythmia, methadone, opioid, QT-interval, toxicity

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## 1. Introduction

Methadone is a synthetic opioid commonly used as a long-acting substitute for maintenance treatment in patients addicted to opioids [1,2]. The benefits of methadone maintenance treatment include reduced mortality, reduced crime, reduced transmission of human immunodeficiency virus (HIV) and viral hepatitis. Due to its properties, it is used as a good choice for methadone maintenance treatment programs (MMTP) for addicted people [3,4]. Although this drug significantly decreases the risk of death from an accidental heroin overdose, there are severe and often fatal side effects following accidental or suicidal use of methadone in the addicted population [5,6]. The analgesic properties of methadone are about 100 times greater than those of morphine. This opioid prevents or reverses withdrawal symptoms and blocks the effects of other opiates' satisfaction and happiness [4]. Despite the benefits of methadone as well as its widespread use in opioid treatment programs and the lack of a suitable alternative to methadone, this drug has a variety of toxic and side effects, even at therapeutic doses, including cardiovascular complications, seizures, respiratory depression, dysphoria, hypoglycemia, meiosis, Gastrointestinal motility disorders and hypothermia [4,7]. The effective dose of methadone is close to its lethal dose, and due to lack of awareness, patients sometimes use this drug more than the therapeutic dose. So that its arbitrary consumption can be harmful; therefore, there have been reports of sudden cardiac death due to this issue [8,9]. Toxic effects of this medication include increased QT interval and polymorphous tachycardia or Tdp, which is a life-threatening arrhythmia [10,11]. Therapeutic doses of methadone (100 mg/day) have also been reported to interfere with normal cardiac repolarization and increase the QT interval. These factors predispose patients to fatal arrhythmias such as torsade de point [1]. Positive genetic factors and congenital QT prolongation syndrome before starting metha-

done play an important role in causing this problem. There are many thresholds for determining the definition of a prolonged QT interval.

Nevertheless, international guidelines state that the sex-linked classification threshold for a QT interval of 450 milliseconds is a risk factor for arrhythmia. Hence, taking a baseline electrocardiogram before treatment and thirty days after the treatment is beneficial [3,12]. Although a cardiac arrest has been reported at high doses, life-threatening arrhythmias have also been reported at doses less than 29 mg daily [13]. Arrhythmias are more likely to occur due to prolongation of the drug-dependent QT interval in patients with an undiagnosed background of other risk factors for QT prolongation such as the presence of congenital prolonged QT syndromes, heart failure, bradycardia, electrolyte disturbances such as hypokalemia, hypomagnesemia, hypocalcemia hypophosphatemia, female gender, old age, hepatic insufficiency, slow metabolism of methadone, use of other QT interval prolonged drug, and Cytochrome P-450 inhibitors such as selective serotonin reuptake inhibitors (SSRIs), antiretroviral drugs and antipsychotics [14]. Methadone poisoning has been a pervasive phenomenon in many countries. This is primarily due to the availability and acceptance of this material in recent years [15]. It should be noted that excessive increases in the duration of this period and the therapeutic dose may have dangerous cardiac effects. The American Academy of Pain Medicine suggests QT interval assessment in patients who orally consume more than 100 mg methadone per day and have a history of cardiovascular disease or are at risk for electrolyte imbalances, and those who are receiving concomitant QT interval-prolonging drugs [16]. Due to the hepatic metabolism of this substance and the low rate of methadone metabolism in Asian race compared to Western countries [17]; this study was performed to determine the frequency of long

QT interval in patients treated with methadone with doses lower than 100 mg referred to the addiction treatment clinic of Razi Medical Center.

## 2. Materials and methods

### 2.1. Inclusion and exclusion criteria

In this cross-sectional study, all the patients in the age range of 30-65 years who were admitted for methadone maintenance treatment to the Razi clinic in Rasht, Iran, during 2016 were enrolled. Patients with a history of using QT-prolonging medications, congenital and non-congenital heart diseases, patients with cardiac dysrhythmia and electrolyte imbalance, major endocrine disorders such as diabetes, hypoparathyroidism, hypothyroidism, and hyperthyroidism, those who consumed alcohol drinks, and patients reluctant to participate were excluded. A group of patients with no history of using methadone was also included.

### 2.2. Data collection

Screening electrocardiography (ECG) was performed for all participants at the beginning of the study. All the ECGs were evaluated and interpreted by two independent cardiologists. Demographic data, addiction history, drug history, QT interval, and Maximum QTc (QT interval corrected with heart rate by Bassett's formula:  $QTc = QT/\sqrt{RR}$ ) and were evaluated. The prolonged QT interval was defined as more than 440 milliseconds and more than 460-450 milliseconds in males and females, respectively. This study was approved by the Guilan University of medical sciences (GUMS) ethics committee with code number IR.GUMS.REC.1395.167.

### 2.3. Statistical analysis

Following examining the normality of quantitative variables using the Kolmogorov-Smirnov test, quantitative data were presented with mean and standard deviation, and qualitative data were reported as frequency and percentage. The mean QT interval was com-

pared with the defined normal value using the ONE SAMPLE T TEST. Also, the mean QT interval based on the methadone dose consumption and other variables was analyzed using T-Test or ANOVA statistical tests. A *P*-value less than 0.05 was considered significant. The statistical analysis was performed using SPSS version 18.

## 3. Results and discussion

Out of 196 subjects, 97 patients were in the methadone group. Regarding demographic characteristics, 83.5% of methadone users and 68.7% of the non-methadone group were males. The mean age of the methadone group was 43.8, and the non-methadone group had a mean of 44.5 years of age, which did not show any significant differences ( $P = 0.08$ ). Demographic data are shown in table 1. The mean of QTc-Max in people who used methadone was  $420.53 \pm 46$  milliseconds, significantly higher than the non-methadone group (mean of QTc-Max in control group =  $380.11 \pm 31$  milliseconds;  $P = 0.001$ ). Also, the T-test showed a significant difference between the mean values of QTc-Max time (milliseconds) in the two groups of methadone users and the non-users group regarding gender ( $P = 0.0001$ ,  $P = 0.0001$ ). So that, the mean of QTc-max in both genders was significantly higher in the methadone group compared to the non-methadone group (Table1). However, within the methadone group, there were not found any significant differences in QT-c max time between men and women.

Table 1- QTc-Max time (millisecond) in methadone users and non-methadone users

	Non-methadone group No (%)		Methadone group No (%)		P-value	
	Normal QT-max	Abnormal QT-max	Normal QT-max	Abnormal QT-max		
Male	67(98.5%)	1(1.5%)	68(84%)	13(16%)	0.002	
Female	30(96.8%)	1(3.2%)	12(75%)	4(25%)	0.04	
Age	30-45years	60(100%)	0(0)	46(80.7%)	11(19.3%)	0.461
	46-55years	35(94.6%)	2(5.4%)	27(87.1%)	12.9(31%)	
	56-65years	2(100%)	0(0)	7(77.8%)	2(22.2%)	

According to the results, there was found a statistically significant difference between the mean of QTc-Max time (milliseconds) in the two groups of methadone users and the non-methadone group in the age groups of 30-45 years and 46-55 years ( $P = 0.0001$  and  $P = 0.0001$ ). However, this difference was not statistically significant in the age groups of 46-55 and 65-56 years ( $P = 0.4$ ,  $P = 0.461$ ). Comparisons of QT-max time between 2 groups regarding gender and age are demonstrated in Table 1. There were 97 methadone users, of which 17.5% had abnormal QTc-Max. Meanwhile, only 2% of the control group had abnormal QTc-Max ( $P = 0.0001$ ). The mean  $\pm$ SD of methadone daily dose used by patients was  $41.04 \pm 13.95$  mg so that the lowest dose was 15 mg and the highest dose was 75 mg/day. Of 97 methadone users, 54 patients consumed fewer than 40 mg per day, and 43 patients used more than 40 mg daily. Of the people who consumed less than 40 mg of methadone daily, 3.7% had abnormal QTc-Max, and among those who consumed more than 40 mg, 34.9% experienced abnormal QTc-Max. The difference was statistically significant ( $P = 0.0001$ ) (Table 2).

Table 2- QTc-Max time (milliseconds) in methadone group in terms of methadone dose

Methadone dose used	Normal QT-max No. (%)	Abnormal QT-max No. (%)	P-value
<40 mg	52(96.3%)	2(6.7%)	0.0001
$\geq$ 40 mg	28(65.1%)	15(34.9%)	0.0001

This study aimed to investigate QT prolongation in patients who consumed methadone less than 100 mg with a maximum of 75 mg per day and a minimum of 15 mg per day. In fact, we aimed to evaluate if it is needed to take more measures, such as taking a baseline and follow up ECG before starting methadone therapy and paying attention to the patient's medications (given that some drugs prolong QT) in doses less than 100 mg daily.

In our study, 97 patients took methadone less than 100 mg, of which 17 people (17.5%) had QTcmax more than the normal limit. On the contrary, of 99 people who did not have a history of methadone usage, only 2% had QTc max more than the normal range, indicating that abnormal QTc max in methadone users was significantly higher than the non-methadone group. Based on the present research results, we concluded that the use of methadone as a maintenance treatment in opium-dependent individuals might have significant cardiovascular effects, including a variety of arrhythmias. We also found that in doses between 40 to 75 mg, the side effects of this substance can also occur. Use of other medications and history of cardiovascular problems, and the duration of methadone use can be decisive in this case. Similar to our findings, results of Fanoie et al. study [17] performed on 450 people, and Anchersen et al.'s study [18] conducted on 200 patients who were treated with methadone showed that methadone usage prolonged the QTc interval and that methadone dose was directly associated with QTc interval prolon-

gation. In the Behnoosh et al. study, methadone overdose was studied in 380 patients. Its side effects, such as decreased level of consciousness, respiratory complications, arrhythmias, hemodynamic disorders, and QTc interval were studied. A significant difference between concomitant use of drugs, duration of methadone use, a prolongation of the QTc interval, and arrhythmia was observed and concluded that initial screening of electrocardiogram changes in order to evaluate prolongation of QTc and arrhythmia should be considered in methadone-treated patients and that concomitant use of drugs or medications that prolong prolongation should be avoided [19]. In a study by Shakoori et al., which was a cohort study investigating 60 volunteers receiving methadone treatment, the methadone dose was measured in three categories, and the QT interval was measured at three specific times. They concluded that methadone therapy increased the patients' QTc interval, but in contrast to our results, there was not found any relationship between the QTc prolongation and dose of the substance and the duration of using methadone [20]. Also, In the study of Isfahani et al., 100 methadone users who received methadone doses greater than 20 mg for 1-108 months were investigated; and according to their result, although an increase in QTc interval was observed, no correlation between the therapeutic dose and the duration of treatment and age of patients with the rate of QTc prolongation was found [1].

The results of the current survey showed that the QTc interval increases with using methadone even in therapeutic doses, and methadone dose was associated with increasing QTc interval; as such, of the people who used less than 40 mg of methadone daily, 3.7% had abnormal QTc-Max. In comparison, of those who received more than 40 mg, 34.9% experienced abnormal QTc-Max. This difference was statistically significant. Therefore, the treatment team needs to be aware

that arrhythmias might occur within a wide range of methadone treatment doses.

There are some limitations to this study. The cross-sectional design of the study limits evaluating casual relationships. Also, it seems that larger studies with a greater sample size might be of value in better investigating the frequency of QT prolongation due to methadone use in different doses.

#### 4. Conclusion

This study showed that methadone therapy increases the QTc interval of patients' ECG. The mean of QTc-Max in people who used methadone was significantly higher than in the non-methadone group. Also, a statistically significant difference was found between the mean of QTc-Max time (milliseconds) in the two groups of methadone users and the non-users group in the age groups of 30-45 and 46-55 years. In addition, it was shown that there was a statistically significant relationship between QTc-Max with methadone dose and indicated that QT prolongation could also happen even in doses of fewer than 100 mg daily.

#### 5. Conflict of interest

The authors declare no conflict of interest.

#### References

- 1- Esfahani MA, Vosoughi AA, Fatehi MH, Shahsanaee A, Teimuri A. Evaluation of QTc interval in Iranian causalities (Janbazan) of Iran-Iraq war receiving maintenance methadone treatment. *Journal of Research in Medical Sciences*. 2012; 17(3): 264-268.
- 2- Katz DF, Sun J, Khatri V, Kao D, Bucher-Bartelson B, Traut C, et al. QTc interval screening in an opioid treatment program. *American Journal of Cardiology*. 2013; 112(7): 1013-1018.  
<https://doi.org/10.1016/j.amjcard.2013.05.037>
- 3-Salimi A, Okazi A. QTC prolongation in acute methadone poisoning. *International Journal of Medical Toxicology and Forensic Medicine*. 2013; 3(4): 135-139.  
[https://doi.org/10.22037/ijmtfm.v3i4\(Autumn\).4559](https://doi.org/10.22037/ijmtfm.v3i4(Autumn).4559)

- 4-Otten EJ. Goldfrank's Toxicologic Emergencies. *Journal of Emergency Medicine*. 2012; 42(2): 239-240.  
<https://doi.org/10.1016/j.jemermed.2011.07.024>
- 5-Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Substance Use & Misuse*. 1996; 31(2): 177-196.  
<https://doi.org/10.3109/10826089609045806>
- 6-Wolff K. Characterization of methadone overdose: clinical considerations and the scientific evidence. *Therapeutic Drug Monitoring*. 2002; 24(4): 457-470.  
<https://doi.org/10.1097/00007691-200208000-00001>
- 7-Sheibani M, Zamani N, Hassanian-Moghaddam H. Electrocardiographic findings in mortalities due to pure methadone toxicity. *Cardiovascular Toxicology*. 2019; 19(1): 62-71.  
<https://doi.org/10.1007/s12012-018-9474-y>
- 8-Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. *Pharmacotherapy*. 2005; 25(11): 1523-1529.  
<https://doi.org/10.1592/phco.2005.25.11.1523>
- 9-Wilcock A, Beattie JM. Prolonged QT interval and methadone: implications for palliative care. *Current opinion in supportive and palliative care*. 2009; 3(4): 252-257.  
<https://doi.org/10.1097/SPC.0b013e328332e0a4>
- 10-Fareed A, Vayalapalli S, Byrd-Sellers J, Casarella J, Drexler K, Amar R, et al. Onsite QTc interval screening for patients in methadone maintenance treatment. *Journal of Addictive Diseases*. 2010; 29(1): 15-22.  
<https://doi.org/10.1080/10550880903436044>
- 11-Hassanian-Moghaddam H, Zamani N. An overview on methadone-intoxicated patients. *Neuropathology of Drug Addictions and Substance Misuse*. 2016; 525-531.  
<https://doi.org/10.1016/B978-0-12-800634-4.00053-6>
- 12-Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. A community-based evaluation of sudden death associated with therapeutic levels of methadone. *American Journal of Medicine*. 2008; 121(1): 66-71.  
<https://doi.org/10.1016/j.amjmed.2007.10.009>
- 13-Hanon S, Seewald RM, Yang F, Schweitzer P, Rosman J. Ventricular arrhythmias in patients treated with methadone for opioid dependence. *Journal of Interventional Cardiac Electrophysiology*. 2010; 28(1): 19-22.
- 14-Golzari H, Dawson NV, Speroff T, Thomas C. Prolonged QTc intervals on admission electrocardiograms: prevalence and correspondence with admission electrolyte abnormalities. *Connecticut Medicine*. 2007; 71(7): 389-397.
- 15-Pani PP, Trogu E, Maremmanni I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. *Cochrane Database of Systematic Reviews*. 2013; 6: CD008939.  
<https://doi.org/10.1002/14651858.CD008939.pub2>
- 16-Ory MG, Ahn SN, Jiang L, Smith ML, Ritter PL, Whitelaw N, et al. Successes of a national study of the chronic disease self-management program: meeting the triple aim of health care reform. *Medical Care*. 2013; 992-998.  
<https://doi.org/10.1097/MLR.0b013e3182a95dd1>
- 17-Fanoe S, Hvidt C, Ege P, Jensen GB. Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. *Heart*. 2007; 93(9): 1051-1055.  
<https://doi.org/10.1136/hrt.2006.100180>
- 18-Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction*. 2009; 104(6): 993-999.  
<https://doi.org/10.1111/j.1360-0443.2009.02549.x>
- 19-Behnoush B, Taghadosinejad F, Salahshour B, Yousefinejad V. Methadone Overdose and Its Complications in Patients Admitted to the Toxicology Emergency Ward of Baharloo Hospital of Tehran in 2011-2012. *Iranian Journal of Toxicology*. 2014; 7(23): 932-939.
- 20-Shakouri H, Zerehsaz MJ, Farajipour S, Salehi A, Salari H, Mohammadkhani M. Effect of Methadone therapy on QTc interval in electrocardiogram of opioid addicted patients. *Journal of Gorgan University of Medical Sciences*. 2014; 16(3): 45-48.