

# Comparing the Effect of Methadone, Buprenorphine, and Opium Tincture on QTc Interval in Addicted Patients Undergoing Maintenance Therapy

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## Research

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# Abstract

**Background :** Methadone, buprenorphine, and opium tincture are effective in the treatment of opioid dependency. Currently, in Iran, these three drugs are used in the maintenance therapy program of opioids. On the other word, there are concerns about the incidence of secondary torsade de point (TdP) arrhythmia caused by the prolonged drug-dependent QTc interval. This cross-sectional study has been designed to evaluate and compare the effects of these three maintenance therapies on the QTc interval.

**Methods :** The study population included 110 patients (85% male with the mean age of  $51.66 \pm 13.34$ ) who participated in an opioid maintenance therapy program for at least 6 months. These patients were assigned to three groups of maintenance therapy with methadone ( $n = 50$ ), buprenorphine ( $n = 30$ ) and opium tincture ( $n = 30$ ). For each patient, a 12-lead ECG was acquired and interpreted. The QT interval was corrected based on the  $QTc = QT + 1/75 (\text{heart rate} - 60)$  formula.

**Results :** The mean QTc interval was  $408.51 \pm 25.88$  msec in the maintenance therapy group with methadone,  $405.58 \pm 20.8$  msec with buprenorphine and  $406.31 \pm 16.9$  with opium tincture. There was no significant difference between the three groups ( $P = 0.83$ ). There was only one case with QTc more than 500 msec (511.25 msec) in the maintenance therapy group with methadone.

**Conclusions :** Methadone, buprenorphine and opium tincture are safe drugs in terms of prolonging the QTc interval and are suitable candidates for maintenance therapy of opioid.

## Background:

Opioid dependence is a chronic state and recurrent clinical disorder with a well-known neurobiological basis (1). It is estimated that, 26.4 to 36.4 million people have opioid misuse worldwide (2). Iran has high rates of opioid addiction in the world. The overall number of opioid misuse in Iran has been estimated to be 4–7 million people (3). There are different treatment methods for the handling of drug dependency (4). Among these treatments, maintenance therapy with an opioid agonist stabilizes the neurochemical status of the brain by substituting short-acting opioids with long-acting opioids as well as stable pharmacokinetic status, like buprenorphine and methadone (1). Although maintenance therapy with opioid is well known worldwide, the selected drug is different in each country. Currently, methadone is considered as the first-line drug in the treatment with agonists in most countries (5). On the other word, according to previous studies, methadone can lead to prolonged QT interval. Prolonged QT interval is followed by increasing risk of torsade de point TdP and ventricular arrhythmia, which can lead to syncope, ventricular fibrillation (VF), and sudden death (6, 7). Nevertheless, due to the relation between the high-dose use of methadone and the incidence of TdP, high-dose use of methadone requires careful monitoring. However, there have been sporadic TdP cases in patients, who receive the recommended dose of methadone (60–100 mg) (5). Apparently, buprenorphine has a lower risk in prolonging the QT interval compared to methadone (6). In a study conducted by Wedam, from 154 participants of a 17-week clinical trial in maintenance therapy with methadone, Levo-Alpha Acetyl Methadol (LAAM) and buprenorphine,

there was a meaningful increase in mean QTc in the LAAM ( $27 \pm 4.8$  msec) and Methadone ( $17.03 \pm 5.0$  msec) group. However, there was no increase in the QTc interval in buprenorphine subjects (8). Nevertheless, the possible association of this drug with prolonged QTc interval is clinically important for some patients, especially in its transdermal application (9).

Opium tincture is considered as one of the drugs suggested for maintenance therapy. In some parts of the western Asia, opium tincture is a culturally appropriate substitute for other treatments such as methadone, and it is somehow a traditional treatment for detoxification and reduction of opioid abandonment symptoms. In Iran, maintenance treatment with opium tincture has been recently introduced as a new strategy towards the treatment of opium consumption (10). However, limited studies have been conducted on the effectiveness and complications of opium tincture to control opium dependence and opium abandonment (11).

The high rate of opioid addiction and consequently the increasing use of maintenance therapy for opioid in Iran require extensive investigations on the possible complications of these methods in the population of the country. On the other word, using opium tincture, as a maintenance therapy, has been only implemented in Iran and its effectiveness and complications require more studies.

## Methods:

In this cross-sectional investigation, 110 patients with opium addiction who referred to substance abuse treatment facility in Bojnurd to be treated with one of the three maintenance therapy methods including methadone, buprenorphine, and opium tincture, were investigated. Considering that there was no ethical justification for not giving any drug or treatment to any group of patients referring to addiction treatment centers, this study did not include a control group.

Sampling was performed non-randomly. Individuals with the following criteria enrolled in our study:

- 1) Subjects (men and women) over 18 years old
- 2) History of opium dependency
- 3) Maintenance therapy with methadone, buprenorphine, opium tincture for at least 6 months
- 4) At least one negative methamphetamine test in the past two months.

Medical history (underlying disease, medication) and demographic information were collected from all volunteers who met the inclusion criteria and then they were examined by a cardiologist. Blood samples, such as K, Ca, AST, ALT, BUN, and Cr, were collected for all volunteers. The exclusion criteria included severe medical illnesses, such as heart failure, renal disease (creatinine clearance  $< 30$  ml/min), and abnormal liver function test, history of hypertension or taking antihypertensive agents, consuming medications affecting QT interval or serum electrolytes, and electrolytic disorders (hypokalemia, hypocalcemia). Then, a 12-leads ECG was taken at rest and 4 h after receiving the last dose of

maintenance therapy. According to the  $QTc = 1/75 (\text{heart rate}-60)$  formula, the QTc was manually modified by a cardiologist. A normal amount of QTc was considered to be  $< 450$  msec in men and  $< 460$  msec in women. The maximum QTc interval in the ECG of each patient was recorded.

## Statistical analysis:

Analytic results were evaluated by the usual statistical method, by the use of IBM SPSS Statistics (IBM, version 24, Chicago, IL, United States). Chi-square test and ANOVA were used to analyze qualitative and quantitative data, respectively. The significance level was set  $P < 0.05$ .

## Results:

In this study, 110 patients were studied (Table 1), 50 (45.5%) of which underwent methadone maintenance therapy, 30 patients (27.3%) underwent buprenorphine maintenance therapy and also 30 patients (27.3%) underwent maintenance therapy with opium tincture. The mean age of the participants is  $51.66 \pm 13.34$  years. The mean age is  $49.83 \pm 13.46$ ,  $47.47 \pm 11.46$  and  $50.50 \pm 13.42$  years in the methadone, buprenorphine and opium tincture group, respectively. According to the ANOVA statistical test, there was no important difference in mean age between groups. ( $P = 0/057$ ).

Table 1  
Demographic and social characteristics of the three participant group

Patient's characteristics		Maintenance therapy with methadone	Maintenance therapy with buprenorphine	Maintenance therapy with opium tincture	P-Value
Sex	Male	41 (82%)	21 (70%)	23 (76.7%)	0.49
	Female	9 (18%)	9 (30%)	7 (23.3%)	
Address	Village	37 (74%)	18 (60%)	18 (60%)	0.33
	Town	13 (26%)	12 (40%)	12 (40%)	
Educational level	Illiterate	8 (16%)	7 (23.3%)	12 (40%)	0.09
	Elementary	18 (36%)	6 (20%)	7 (23.3%)	
	Junior high school	10 (20%)	9 (30%)	1 (3.3%)	
	Senior high school	2 (4%)	1 (3.3%)	1 (3.3%)	
	Diploma	8 (16%)	7 (23.3%)	5 (16.7%)	
	Associate degree	3 (6%)	0	4 (13.3%)	
	Bachelor	1 (2%)	0	0	
Marital status	Married	45 (90%)	25 (83.3%)	25(83.3%)	0.52
	Single	0	1 (3.3%)	1 (3.3)	
	Divorced	1 (2%)	2 (6.7%)	4 (13.3%)	
	Widow	4 (8%)	2 (6.7%)	0	
Method of use	Inhalation	35 (70%)	25 (83.3%)	15 (50%)	0.11
	Oral	3 (6%)	1 3.3%)	5 16.7%)	
	Injection	0	0	0	
	Inhalation-oral	11 (22%)	4 (13.3%)	10 (33.3%)	

Among the participants, 85 (77.3%) were male and 25 (22.7%) were female. Based on the Chi-Square, there was no meaningful difference in terms of sex distribution between the groups.

There were no abnormalities in the ECG evaluation of the patients. The mean QTc interval in all participants was calculated  $407.1 \pm 22.22$  and the mean QTc was  $405.8 \pm 23.1$  and  $411.54 \pm 18.64$  for all men and women, respectively. The mean QTc in the groups by sex segregation are compared in the table.

According to Table 1 and based on the ANOVA statistical test, there was no statistically significant variation between three groups in QTc mean age.

In this study, abnormal QTc values have been considered  $< 460$  msec and  $< 450$  msec in women and men, respectively. Accordingly, the frequency of abnormal QTc in the male subjects was one case with QTc = 511/25 msec (minimum QTc in men was 36/5/363 and maximum QTc was 511/25 msec) and there was no abnormal QTc in the female subjects (minimum QTc in women was 369 msec and maximum QTc was 449 msec). Table 2 shows mean QTc (msec) in each therapy group.

Table 2  
Mean QTC in each maintenance therapy group

	Mean QTC in maintenance therapy with opium tincture	Mean QTC in maintenance therapy with buprenorphine	Mean QTC in maintenance therapy with methadone	F	P-value
Female	$410.82 \pm 56.1$	$409.44 \pm 27.16$	$414.19 \pm 16.37$	0.13	0.86
Male	$404.91 \pm 18.92$	$403.92 \pm 17.97$	$407.26 \pm 27.53$	0.15	0.84
Total	$406.31 \pm 16.9$	$405.58 \pm 20.8$	$408.51 \pm 25.88$	0.19	0.82

## Discussion:

In this study, from the 110 participants, 50 participants underwent maintenance therapy with methadone. In this group, the mean age was  $51.66 \pm 13.34$  years and there were 41 men. The mean QTc was  $408.51 \pm 25.88$  msec in this group and there was only one case with QTc  $> 500$  msec (511.25 msec). Numerous studies have investigated the effect of methadone on the QTc interval, which have led to conflicting results in this field. In a cross-sectional study by Peles conducted on 138 patients undergoing maintenance therapy with methadone (98% male and with mean daily methadone dose of  $170.9 \pm 50.2$  mg), the mean QTc was calculated to be  $418.3 \pm 32.8$  msec and there have been only three cases with QTc  $> 500$  msec (12). In another cross-sectional study performed on 104 patients undergoing maintenance therapy with methadone (61% male with average daily methadone dose of 110 mg) the mean QTc was measured to be 428 msec, and although 33% of patients had prolonged QTc, none of them had QTc  $> 500$  msec (13). On the other word, in a study by Maremmanni, which was implemented on 83 addicts undergoing maintenance therapy with methadone for at least 6 months, 83% of patients had prolonged QTc and there were two cases with QTc  $> 500$  msec (14).

In this study, maintenance therapy with methadone was concluded to be safe and it had no association with TdP. However, in a study by Ehret, there have been cases of TdP in addition to the high prevalence of

prolonged QTc in patients undergoing maintenance therapy with methadone (15). On the other hand, in studies conducted by Gheshlaghi (16), Mercadante (17), and Krantz (18), in which patients had baseline and follow-up ECGs, despite prolonged QTc intervals in follow-up ECGs compared to baseline ECG, the mean QTc has been still normal, which is similar to the findings of our study. All three studies support the conclusion of this study, in which there is a low risk of methadone in the incidence of serious arrhythmia.

From 110 study participants, 30 patients were undergone maintenance therapy with buprenorphine, with a mean age of  $47.53 \pm 11.46$  years that 21 of whom were male. The mean QTc was  $405.58 \pm 20.8$  msec. There was no prolonged QTc in this treatment group. So far, most studies, which were conducted on the effect of buprenorphine on QTc interval, support the findings of our study that buprenorphine is not followed by prolonged QTc. Most of the studies have compared the impact of maintenance therapy with buprenorphine on the QTc interval between methadone and buprenorphine. In the Anchersen study, 29% of the 173 patients, who were treated with methadone, had QTc > 450 msec and 15% had QTc > 470 msec; however, none of the patients treated with buprenorphine had QTc > 450 msec (19). In another study, Sabrina has exclusively investigated the effect of buprenorphine on QTc interval and calculated QTc changes in the follow-up ECG compared to baseline ECG. In that study, buprenorphine was also associated with slight changes in QTc in some patients, which is consistent with the findings of our study (6).

In our study, 30 participants underwent maintenance therapy with opium tincture. The mean age of this group was  $50.83 \pm 13.42$  years and 23 of them were male. In the opium tincture group, the mean QTc was calculated to be  $406.31 \pm 16.9$  msec. None of the patients in this group had prolonged QTc. Given that maintenance therapy with opium tincture is only used in Iran and has a short life span, there are no studies on its effects on QTc interval and further studies are needed. Unlike the findings of our study, in most comparative studies between maintenance therapy with methadone and buprenorphine, such as the studies of Fareed (20), Wedam (8) and Fanoie (21), methadone has been associated with a greater risk of prolonged QTc interval. In these studies, buprenorphine has been suggested as the first-line strategy for opioid maintenance therapy. On the other hand, in a comparative study conducted by Stallvik (22), although the QTc interval was more changed in the follow-up ECGs in the methadone group compared to the buprenorphine, there were no cases with prolonged QTc in both methadone and buprenorphine groups, which indicate consistency with the findings of our study.

## Conclusions:

Given the findings of our study, none of the three maintenance therapy methods with methadone, buprenorphine and opium tincture resulted in prolonged QTc interval and increasing risk of TdP arrhythmia. Moreover, in the statistical analysis, there was no meaningful difference in the average QTc among the three groups undergoing maintenance therapy ( $P = 0.82$ ) indicating similar effects of all three treatment methods on QTc.

Limitations: Due to the low compliance of addicted patients and their lack of regular referral to substance abuse treatment facilities, this study was cross-sectional and the changes in QTc intervals were not investigated before and after maintenance therapy. The sample size collection from the patients undergoing maintenance therapy with buprenorphine and opium tincture was limited. Because of the limited sample size, it was not possible to further match patients, especially in terms of sex and mean age.

## **Recommendation:**

In recent years, opium tincture has been used as maintenance therapy for addicted patients, only in Iran. It is recommended to conduct further studies on the effect of this treatment method on QTc interval. It is also suggested to compare these three treatment methods in a larger population of addicted patients undergoing opium maintenance therapy.

It is offered to calculate the changes in QTc intervals for each patient before and after treatment by taking ECG and before and after maintenance therapy. It is suggested to match the patients in terms of sex, mean age, and other factors affecting QTc in future comparative studies.

## **List Of Abbreviations**

Torsade de point (TdP)

Ventricular fibrillation (VF)

Levo-Alpha Acetyl Methadol (LAAM)

## **Declarations**

### **Ethics approval and consent to participate:**

In this study, patients undergoing maintenance therapy for addiction treatment were enrolled, and there was no additional intervention during the treatment of cases. No separate blood sampling was performed in this research, and blood tests and electrocardiograms were added to the periodic routine tests. All volunteers received written consent before starting the study.

In compiling the demographic information questionnaire, private and confidential questions were attempted as far as possible and patients' consent to cooperate to complete the questionnaire was obtained. The questionnaire does not have a full name. The present questionnaire has no other ethical considerations due to the lack of intervention in this study.

Review Board of the North Khorasan University of Medical Sciences approved the study. All subjects were informed about the study and all provided informed consent.



**Consent for publication:** I, Leila Hosseini, the corresponding author of this article declare that I have taken a permission note from the patients to publish the paper.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors’ contribution:** All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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