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Opioids and Cardiac Arrhythmia: A Literature Review

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Significance of the Study

- Opioids are widely used throughout the world and statistics show that sales of prescription opioids in the United States nearly quadrupled from 1999 to 2014. One of the most common side effects of opioids is their influence on the electrical activity of the heart. In this review, results and reports from previous studies are investigated. We confirm that from the perspectives of prolongation of QT interval and arrhythmogenicity, opioids such as methadone even in low doses are high-risk drugs, tramadol and oxycodone show intermediate risk and opioids such as morphine and buprenorphine are low-risk drugs. This review may serve to increase the understanding of physicians and pharmacists regarding effects of opioids on heart electrical activity and their safety levels to decide on prioritizing the administration of these drugs in different patients, especially in opioid-dependent persons. It can also be a guide for students and researchers interested in studies on opioid drugs.

Keywords
Opioids · Electrocardiogram · QT prolongation · Cardiac arrhythmia

Abstract
Objective: One of the most important side effects of opioids is their influence on the electrical activity of the heart. This review focusses on the effects of opioids on QT interval prolongation and their arrhythmogenic liability. ***Methods:*** By using various keywords, papers published up to 2018 in different databases were searched and identified. The search terms were opioids names, corrected QT interval, human-ether-a-go-go gene, torsades de pointes (TdP), cardiac arrhythmias, opioid dependence and other relevant terms. It emphasized the effects of each opioid agent alone on electrocardiogram (ECG) and some interactions. ***Results:*** Available data indicate that some opioids such as methadone are high-risk even at low doses, and have potential for prolongation of the QT interval and development of TdP, a dangerous ventricular tachycardia. A number of opioids such as tramadol and oxycodone are intermediate risk drugs and may develop long QT interval and TdP in high doses. Some other opioids such as morphine and buprenorphine are low-risk drugs and do not produce QT interval prolongation and TdP at least in routine doses. Opium-consumers are at higher risk of supra-ventricular arrhythmias, sinus bradycardia, cardiac block and atrial fibrillation. ***Conclusion:*** The cardiac arrhythmogenicity of various opioids is different. Methadone has a higher capability to induce long QT interval and dangerous arrhythmias in conventional doses than others. To reduce of arrhythmogenic risk, high doses of opioids must be used cautiously with periodic monitoring of ECG in high-risk consumers such as patients under opioid maintenance treatment.

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Introduction

Opioids are a drug class with pain relieving property originating from 3 sources. Some of them, named as opiates, are derived from opium. Morphine is one of the direct opium derivatives, and heroin is a semi-synthetic derivative of morphine. Endogenous opioids such as endorphins are produced in the body and some opioids like methadone and pethidine are synthetic. There is an extensive consumption rate for opioids worldwide. In medicine, opioids are used for relieving of severe pain, in anaesthesia as ancillary drugs, and maintenance therapy in opioid withdrawal syndrome. Opioid substitution is an effective method for the treatment of opioid-dependent persons. The aims of this intervention are to decrease the risk of drug-related death, the incidence of criminal activity, the use of illicit or non-prescribed drugs, the risk of transmitting HIV, hepatitis B and C virus, the duration of episodes of drug misuse and to improve overall personal, social and family functioning and to assist public health [1, 2].

Because of their euphoric effects, opioids are attractive substances [3, 4]. Opioids exert their pharmacological and physiological activities predominantly through 3 main classes of opioid receptors; mu, kappa and delta. The most commonly used opioids in opioid maintenance treatment (OMT) and chronic pain treatment are mu agonists such as methadone, morphine and buprenorphine [5, 6].

Numerous studies have investigated the harmful effects of opioids on the body organs especially the cardiovascular system. The main side effects of opioids include nausea, vomiting, constipation, headache, respiratory depression, decreased cardiac output (especially when applied with benzodiazepines), bradycardia, histamine release, heart electrical disturbance and cardiac arrhythmia and so on [7–10]. Perhaps the most common cardiac side effect of opioids is the prolongation of the QT interval, which can lead to torsades de pointes (TdP), which is a kind of ventricular tachyarrhythmia with the potential of causing sudden death [11–13]. The significance of this side effect is such that in recent years, most of the drugs have been restricted or withdrawn from the market due to this side effect [14]. Moreover, in drug development according to FDA recommendations, all new drugs having systemic bioavailability prior to approval should be examined for their impact on QT interval prolongation [15].

Methods

By using 20 opioid names, all relevant papers published by the end of 2017 in different databases such as Pubmed and Scopus were searched and identified. Names of opioid including "Buprenorphine," "Methadone," "Morphine," "Hydromorphone," "Oxycodone," "Tramadol," "Codeine," "Loperamide," "Tapentadol," "Oxymorphone," "Hydrocodone," "Pethidine," "Levorphanol," "Levo-alpha-acetylmethadol (LAAM)," "Fentanyl and its analogs" and "Opium" along with "corrected QT interval (QTc)," "QT interval," "QT prolongation," "ventricular arrhythmias," "atrial arrhythmias," "hERG," "TdP" and "other related terms." Each paper was screened for relevance to the arrhythmogenicity and electrocardiogram (ECG) side effects of opioids. Some information was obtained from some other studies that were not directly related to the topic but helped to better understand the content.

QT Interval

The QT interval is defined as the time between the start of the Q wave and the end of the T wave which is the electrical presentation of ventricular depolarization and repolarization in ECG (Fig. 1). The prolongation of the QT interval indicates that electrical conduction in the ventricles is abnormally slow (Fig. 1). Since the QT interval varies with heart rate, there are several formulas to correct the QT interval for heart rate like Bazette's, Fridericia's, and Framingham's formulas. One of the most common of them is Bazette's formula ($QTc = QT/\sqrt{RR}$) where RR is the distance between the top of 2 consecutive R waves [16] (Fig. 1). QTc (heart rate-corrected QT) interval greater than 450 ms in males, and greater than 470 ms in females (or QTc greater than 0.44 s) and ΔQTc greater than 30 ms is considered to be prolonged regardless of the correction formula used [17]. QTc greater than 500 ms is an important risk factor for TdP, which is a ventricular tachyarrhythmia presenting with palpitation, which can lead to syncope and seizure. TdP is often self-limited but sometimes turns into ventricular fibrillation, a life-threatening arrhythmia that may cause sudden death [18].

Mechanism of Drug-Induced Prolongation of QT Interval

Prolongation of QT interval is associated with prolonged cardiac repolarization that is initiated by rapid outflow of potassium (K+), through the cardiac rapid-rectifying K+ channel. This channel is encoded by human-ether-a-go-go gene (hERG; KCNH2) and its blocking by some agents is a prominent mechanism for prolonging of the QT interval [19, 20]. However, there are several underlying conditions that can predispose a drug-abuser to QT prolongation events such as cardiac disease, female gender and HIV infection. Also some drugs such as some of the antiretroviral protease inhibitors (ATV, RTV, IDV), antifungals azole agents (ketoconazole, fluconazole and itraconazole) and some macrolide antibiotics (erythromycin, clarithromycin, dirithromycin, roxithromycin) by inhibition of CYP3A4, methadone and buprenorphine metabolizing enzyme, can result in higher levels of these agents and leads to prolongation of QT interval which however is not the focus of this study [21]. This review aims to inspect effects of some opioids, available in the market, on QT interval and arrhythmogenic susceptibility.

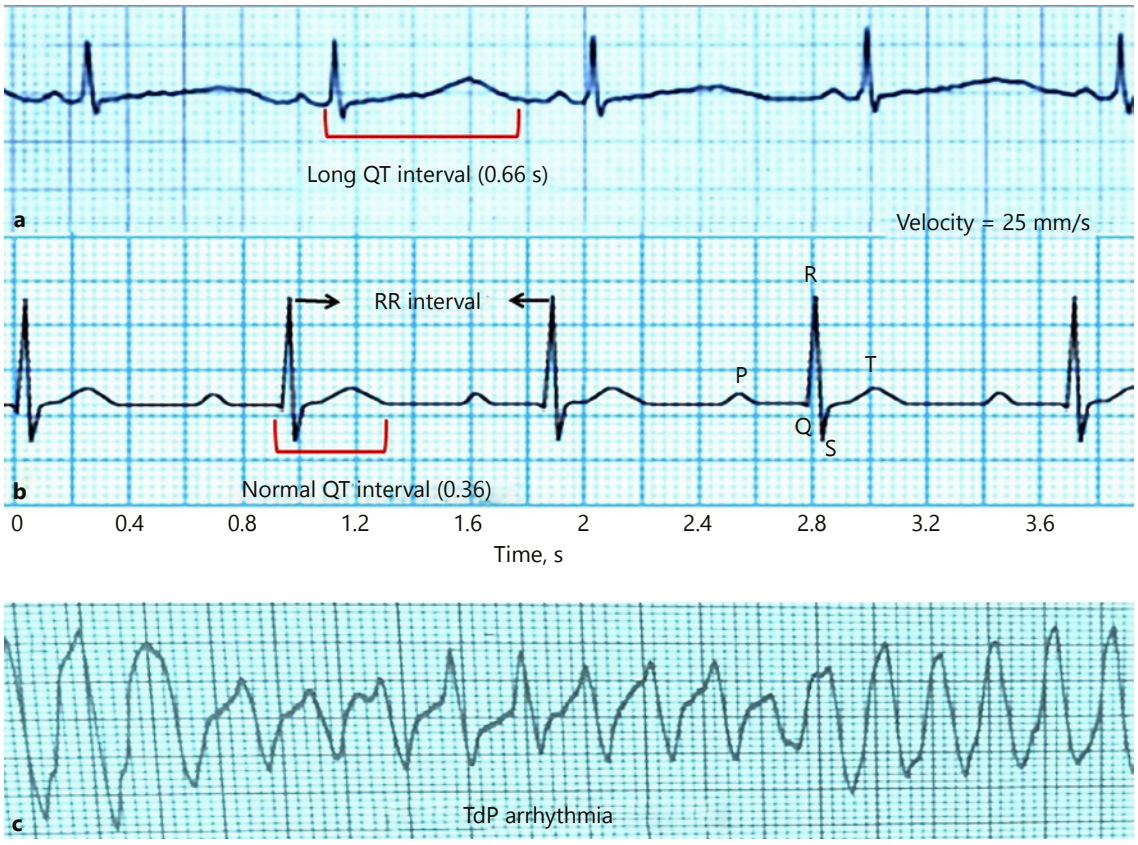

Fig. 1. a An ECG trace of lead II with long QT interval (66 ms). **b** A normal trace of an ECG in which ECG waves (P, QRS and T) are shown and QT interval is in normal range (0.36 s). QT interval is a measure of the time between the onset of the Q wave and the end of the T wave in the ECG and includes both electrical depolarization and repolarization periods of the ventricles. R is a point corresponding to the peak of the QRS complex of the ECG; and RR is the interval between successive Rs. **c** A trace of TdP arrhythmia, a specific form of polymorphic ventricular tachycardia in patients or animals with long QT interval characterized by rapid, irregular QRS complexes, which appear to be twisting around the ECG baseline. This arrhythmia may cease spontaneously or lead to ventricular fibrillation. TdP, torsades de pointes.

Clinical Management of QT Prolongation

In patients prone to QT prolongation, prevention if at all possible, is the first action. Use of drugs that prolong the QT interval should be minimized, and potential drug interactions with QT-prolonging drugs are considered [22]. Some agents by themselves may produce mild prolongation of QTc but when used with other medications that inhibit their metabolism (e.g., terfenadine and cisapride), significant prolongation can occur [23]. The worst situation is when QT prolongation leads to torsade de pointes. The range of clinical manifestations in this arrhythmia varies from asymptomatic self-limiting dysrhythmia to cardiac arrest. Immediate treatment can be divided into pharmacologic treatment (magnesium or isoproterenol) and nonpharmacologic procedures (cardiac pacing or defibrillation with unsynchronized shock) [24]. The goal of treatment is to increase heart rate, shortening of QT interval and the prevention of abnormal repolarization or early after depolarization. After initial treatment, predisposing factors should be compensated (e.g., electrolyte disturbances) or eliminated (e.g., drugs eliciting QT prolongation) [22].

Prolongation of QT Interval and Ventricular Arrhythmia

Buprenorphine

Buprenorphine is a semi-synthetic partial mu receptor agonist which dissociates the receptor slowly. Therefore, it has a prolonged duration of effect, and based on this property, buprenorphine is used in OMT and to decrease pain. It is also a kappa receptor antagonist, a delta receptor agonist and a partially nociceptin receptor agonist. The potency of buprenorphine is about 25–100 times that of morphine [25]. Several studies have investigated the effects of buprenorphine on QT interval and TdP, and almost all studies suggest that treatment with buprenorphine (3 mg) is safe and has no effect on QT interval [26–28]. In one of the most recent studies on 58 subjects, Darpo et al. [26] demonstrated that concentrations of plasma buprenorphine under 5 ng/mL do not prolong corrected QT (QTc) interval above the level of clinical concern. A study on rats indicated that subcutaneous administration of buprenorphine in doses of 0.006, 0.03 and 0.15 mg/kg reduces QT time and increases heart rate. This dose-de-

pendent effect is reversible at low and medium doses (0.006, 0.03 mg/kg) but not at high doses (15 mg/kg) [27]. In the United States, buprenorphine is mostly supplied in combination with naloxone. Baker et al. [28] studied the effect on QT interval, of buprenorphine/naloxone, alone and in parallel with antiretroviral (ARV) agents, and did not observe a clinically significant increase in QT interval. However, when used along with antiretrovirals, the increase in QT interval was statistically significant [28]. Demarie et al. [29] studied the risk of TdP in 190 substance-abuse patients (cocaine, heroin and alcohol abusers). Of 94 cases on methadone maintenance treatment (MMT), 29 patients were on buprenorphine maintenance treatment (BMT) and 67 patients were not receiving any treatment. They concluded that buprenorphine does not cause TdP and is a safe alternative for methadone and morphine in OMT [29]. Wedam et al. [30] designed a double-blind clinical trial to compare the effect of levomethadylacetat (or LAAM), methadone and buprenorphine on QTc. All these drugs are hERG blockers. Among the 165 opioid-dependent patients included in the study, 54 of them received buprenorphine and no significant QTc prolongation was observed; they suggested buprenorphine as a safe alternative [30]. The results of a retrospective study between 1967 and 2011 on 4418215 adverse events, of which 7283 of them were buprenorphine cases and 14915 of them were methadone cases, indicate that buprenorphine is a safer drug than methadone because it was associated with less prevalence of cardiac arrhythmias as 1.8% for ventricular arrhythmia, 0.3% for QT prolongation and 0.1% for TdP in comparison with methadone, which showed 11.6% for ventricular arrhythmia, 2.6% for QT prolongation and 1.7% for TdP among users [31]. Supporting this conclusion was another study on 73 patients on BMT and 55 patients on MMT. In this study, Fareed et al. [32] compared QTc prolongation in both groups over a 5-year period; their results demonstrated that unlike methadone, buprenorphine has no significant effect on QTc prolongation and is a safer drug for OMT than methadone. Also in 12 patients who had QT prolongation and ventricular arrhythmia due to methadone, changing methadone to buprenorphine in 3 of them made the QT interval normal and augmented the preference for buprenorphine over methadone [33]. Regarding the effect of different doses of buprenorphine, in a cross-sectional study on 450 heroin-dependent who were under BMT (43 patients) or MMT (407 patients), the results showed no association between buprenorphine dose and QTc prolongation, and the patients on BMT had neither QT nor QTc prolongation [34]. In another study, 27 patients out of 173 patients on OMT received buprenorphine and none of them had QTc interval more than 450 ms and there was a relationship between buprenorphine dose and QTc interval [35]. Stallvik et al. [36] studied 80 OMT patients of whom 35 received BMT; they obtained the same result; none of the patients had QTc interval more than 450 ms and no association with serum concentration of buprenorphine was seen. Another study indicated that buprenorphine is a safe drug in common daily doses (11 ± 5 mg) [37]. Encouraging the idea of choosing buprenorphine over methadone, a case report showed that buprenorphone was able to settle QT prolongation and ventricular arrhythmia secondary to methadone [38]. Thus, based on the studies mentioned above, buprenorphine at conventional doses, by itself, does not appear to produce clinically significant QT interval prolongation and arrhythmia, and is a safe drug in this respect.

Methadone

Methadone is a synthetic mu receptor agonist that is used in OMT and pain treatment (7). Because of its efficacy, cost effectiveness and dose flexibility, methadone is the most extensively used drug in the treatment of opioid-dependency [39, 40]. In addition to some serious side effects like oedema and hypotension, the more important concern is its QT prolongation effect, which can lead to TdP as a potentially lethal arrhythmia [41–43]. Some of the reports in this regard have been summarized in Table 1. In a recent study, Romero et al. [44] surveyed 2,735 patients with prolonged QT 89% of whom presented TdP. These patients had a history of using several kinds of prescription drugs and the authors concluded that methadone is the leading medication that can cause TdP among the prescription drugs [44]. In 2004, 10 cases with prolonged QT interval were reported of whom 3 of them showed TdP. Two of the patients presented with ventricular tachycardia, and premature ventricular contraction (PVC) bigeminy happened to one of them. All these 10 patients were on oral MMT (dose range 14–360 mg/day), and except one all of them were on drugs other than methadone, which had pharmacological interactions with methadone [45]. Also, there is a case report of ventricular bigeminy after receiving methadone, voriconazole and esomeprazole in a patient with lymphoblastic leukaemia, which suggests that interactions between these drugs caused high levels of methadone in the plasma led to arrhythmia [46]. There are other reports of TdP in patients who were on MMT and other interacting drugs together. For example, in 3 case reports, TdP was observed in patients who were on both methadone and cocaine, which are known agents with QT interval prolongation effect [47–49]. Butler et al. [50] studied the cardiac arrhythmia-related death in 14,500 MMT patients and showed that the cardinal reason for death in these patients was taking other prescription drugs beside methadone. These results are supported by another study which showed that the combination of methadone- interacting drugs with methadone has a greater probability of causing QT prolongation and TdP [51].

With the aim of studying the relation of QT prolongation and opioid use, there are several studies that compare buprenorphine to methadone. For example, in an earlier study, of 165 OMT patients, 55 patients enrolled to each group of methadone, buprenorphine and LAAM; The LAAM and methadone group had a significant QT prolongation [30]. The retrospective pharmacoepidemiological study of Kao et al. [31] in which 14,915 patients received methadone showed a proportionate association between methadone and ventricular arrhythmias, while buprenorphine was a safer drug. The investigation of QT prolongation in 73 BMT patients and 55 MMT patients revealed significant QT prolongation in MMT patients over 5 years in comparison to buprenorphine receivers [30]. Several cross-sectional studies indicated that methadone is associated with prolonged QT interval (longer than 430 ms for males and 450 ms for females) [52–57]. Some other studies investigated the possible relationship between the dose of methadone and QT prolongation, and concluded that there is a wide range of dosage in which QT prolongation and TdP occur (65–1,100 mg/day) and the magnitude QT prolongation is more likely in high doses of the medication [58]. Gil et al. [59] studied 4 HIV patients with TdP arrhythmia who were receiving antiviral therapy and very high doses of methadone (mean 415 mg/day); they suggested a dose-dependent effect of methadone on QT interval prolongation [59]. Receiving very high doses of methadone (600 mg/day), along with interacting drugs through CYP3A4 iso-

Table 1. Selected major studies indicating the methadone, buprenorphine, LAAM and oxycodone arrhythmogenicity

Type of study	Formula for QT correction	TdP/QT ≥500 ms	Study population	Main finding	References
Retrospective	Unreported	0.1% (1 case) of buprenorphine cases showed TdP versus 1.7% of methadone cases	Methadone group: 14,915 Buprenorphine group: 7,283 All other cases of adverse events: 4,796,017	132 (1.8%) ventricular arrhythmia/cardiac arrest, 19 (0.3%) QTc prolongation/torsade de pointes cases associated with buprenorphine, 1,729 (11.6%) ventricular arrhythmia/cardiac arrest and 390 (2.6%) QTc prolongation/torsade de pointes cases involving methadone; Buprenorphine is suggested as a safer drug than methadone regarding ventricular arrhythmia and TdP	Kao et al. [31], 2015
Retrospective	Unreported	At the end of study (2012) 10% of methadone group had QTc above 500 ms; But they also had congestive heart failure(not mentioned the exact percent)	Methadone group: 55 Buprenorphine group: 73 (for OMT)	Methadone maybe associated with QTc prolongation (QTc more than 450 ms) while buprenorphine is not associated with QTc prolongation (QTc less than 450 ms) over a five-year period, consuming methadone and congestive heart failure are risk factors for QTc more than 500 ms	Fareed et al. [32], 2013
Cohort	Bazette's formula	No QT above 500 ms	Methadone group: 42 (for MMT) No control group	Four patients developed QTc prolongation. Methadone is able to prolong QTc interval at doses under 100 mg/day	Perrin-Terrin et al. [51], 2011
Randomized double-blind clinical trial	Bazette's and Fridericia's formula	10% of both groups methadone and LAAM had QTc above 500 ms and non in buprenorphine group had QTc above 500 ms	High dose methadone group: 55 LAAM group: 55 Buprenorphine: 55 (for OMT) No control group	Buprenorphine is associated with less QT prolongation, comparing to methadone and levomethadyl which had significant prolongation of more than 30 ms in QTc	Wedam et al. [30], 2007
Cross-sectional	Bazette's formula	No QT above 500 ms	Methadone group: 104 (for MMT and chronic pain) No control group	33% of subjects had QT prolongation Significant dose response was observed between QTc interval and higher doses and shorter duration of methadone	Cruciani et al. [52], 2005 (measurment)
Cross-sectional	Bazette's formula	2.4% (two subjects) had QT interval above 500 ms	Methadone group: 83 (for MMT)	81% of subjects had QT prolongation; Relative to age and sex, there was no association between methadone dose and QT	Maremmani et al. [53], 2005
Cross-sectional, prospective	Bazette's formula	3 patients had QTC above 500 ms who 2 of them dies but not from a cardiac origine	Methadone group: 138 (for MMT)	No relationship was seen between methadone dose and methadone serum level with QTc prolongation, and the authors suggested MMT is safe and only in high doses (over 120 mg/day) monitoring is needed	Peles et al. [54], 2007
Cross-sectional	Bazette's formula	2 patients (1.8%) had QTC above 500 ms	Methadone group: 109 (for MMT) No control group	10 patients (9.2%) had prolonged QTc (above 440 ms) but there were significant differences between these ten and the ones who didn't developed QTC prolongation; There was a correlation between methadone dose and QTc prolongation but it's not significant between serum level of methadone and QTc interval	Fonseca et al. [55], 2009
Cross-sectional	Bazette's formula	No QT above 500 ms	Methadone group: 155 (83 subjects had ECG and 72 subjects did not have ECG) (for MMT) No control group	Three-quarter of 155 subjects needed ECG monitoring when prescribing methadone according to MHRA criteria, 18.1% of 83 subjects had QTc prolongation; QTc length was associated with methadone dose	Mayet et al. [56], 2011
Cross-sectional	Bazette's and Fridericia's formula	No QT above 500 ms	Methadone group: 25 Oxycodone group: 27 Morphine group: 23 Tramadol group: 16 (for chronic pain)	First study which demonstrated the association between oxycodone and QTc and also confirmed the association between methadone and QTc. higher doses of oxycodone and methadone is related with longer QTc	Fanoe et al. [78], 2009

Table 1. (continued)

Type of study	Formula for QT correction	TdP/QT ≥500 ms	Study population	Main finding	References
Cross-sectional	Bazette's formula	No QT above 500 ms	Total 511 subject which: slow-releasing morphine group: 66% methadone group: 20% buprenorphine group: 13% codeine group: 2% liquid morphine: 1%	The most frequent ECG abnormalities in opiate addicts is ST abnormalities, QTc prolongation and tall R- and/or S-waves	Wallner et al. [57], 2008
Retrospective	Unreported	43 subjects (0.78%) developed TdP	5503 subjects with adverse events associated with methadone	A wide range of methadone dose can cause QT prolongation	Pearson et al. [58], 2005
Retrospective case-series analysis	Bazette's formula	No QT above 500 ms	Methadone users: 17 (for chronic pain and MMT) no control group	There is a relationship between methadone dose and QT interval	Krantz et al. [62], 2003
Prospective (chart review)	Bazette's and Fridericia's formula	No QT above 500 ms	Methadone users (IV): 47 Morphine users: 35 (for cancer pain) no control group	IV Methadone (methadone + chlorobutanol) is associated with QT interval prolongation	Kornick et al. [63], 2003
Case-control, Retrospective	Bazette's formula	16.2% had QTc above 500 ms and 3.6% had TdP	Methadone group: 167 (Cancer pain) control: 80	QT prolongation was associated with higher methadone dose	Ehret et al. 2006
Prospective	Bazette's formula	No QT above 500 ms	Methadone users: 160 (for MMT) no control group	There was positive correlation between serum level of methadone and QT magnitude	Martel et al. [64], 2005 (impact)
Cross-sectional	Bazette's formula	4.6% (8 subjects) of methadone group had QTc above 500 ms	Methadone group: 173 Buprenorphine group: 27 (for OMT) no control group	28.9% of methadone group had QTc above 450 ms and all patients in buprenorphine group had QTc under 450 ms. there was a positive dose dependant relationship between methadone dose and QTc length	Anchersen et al. [35], 2009
Cross-sectional	Bazette's formula	No QT above 500 ms	Buprenorphine users: 43 methadone users: 407 no control group	No association between buprenorphine and QTc was observed. 28% of men and 32% of women in methadone group had QTc prolongation; methadone dose was associated with longer QT interval	Fanoe et al. [78], 2009
Retrospective	Hodges formula	QTc above 500 ms was seen during 14.1% of encounters	Methadone group: 259 (562 encounters) No control group	The dose dependent correlation between QTc and methadone was weak; Prevalence of prolonged QTc (25.6% of encounters) among methadone group was high but prevalence of ventricular arrhythmia (3.4%) was relatively low	Chowdhury al. [66], 2015
Cross-sectional	Bazette's formula	No QT above 500 ms	Methadone group: 180 (for MMT) no control group	11.15 (20 subjects) had QT above 450 ms; the association between QTc prolongation and methadone use was significant, and no significant association between methadone dose and QTc was found	Roy et al. [67], 2012
Prospective	Bazette's formula	No QT above 500 ms	Methadone group: 45 Buprenorphine group: 35 (for OMT) no control group	No QTc above 450 ms in both groups was seen, and no association between QTc and serum concentration of neither methadone nor buprenorphine was detected. methadone does not cause QTc prolongation in doses below 100 mg/day. Buprenorphine is a safe alternative for methadone	Stallvik et al. [36], 2013
Retrospective	Unreported	Four patients of methadone group had QTc above, no TdP	Methadone group: 90 (for chronic pain) control group: 40	36.7% of methadone group had QTc more than 450 while 7.5% of control group had prolonged QTc, no relationship between methadone doses, serum level or duration of treatment was observed	Huh et al. [68], 2010

Table 1. (continued)

Type of study	Formula for QT correction	TdP/QT ≥500 ms	Study population	Main finding	References
Retrospective	Unreported	No QTc above 500 ms	Methadone group: 7 (for chronic pain) no control group	No association between QTc and methadone dose or duration of use was found	Anghelesc et al. [69], 2016
Retrospective	Unreported	29 patients (6%) had QTcabove 500 ms	Methadone group: 1,246 (for chronic pain) no control group	49.4% had QT prolongation, especially in old-age patients and methadone doses more than 100 mg/day	Price et al. [70], 2014
Retrospective	Unreported	7 subjects had QTc above 500 ms	Methadone cases: 51 (for chronic pain)	ECG monitoring before therapy with methadone is necessary	Mcnamara et al. [71], 2011
Prospective	Bazette's formula	5% had QTc above 500 ms	Methadone group: 130 (for chronic pain) no control group	5% of patients had QTc above 500 ms and were in serious risk of TdP; ECG monitoring one week after methadone dosage increased is advised	Van den Beuken-van Everdingen et al. [72], 2013
Prospective	Bazette's formula	1 subject had QTc above 500 ms	Methadone group: 82 (for pain) control group: 102	Methadone is associated with QTc prolongation at the first month of initiating therapy with methadone but this association doesn't exist at third and sixth month of treatment	Grodofsky et al. [73], 2015
Prospective	Bazette's formula	No QTc above 500 ms	Methadone group: 8 (for chronic pain)	Switching from low doses of oral morphine to analgesic doses of oral methadone causes significant QTc prolongation. QTc prolongation after 9 month of treatment with methadone is not significant	Fredheim et al. [74], 2006

LAAM, levo-alpha-acetylmethadol; TdP, torsades de points; QTc, corrected QT interval; MMT, methadone maintenance treatment; OMT, opioid maintenance treatment.

enzyme system, caused TdP in 3 patients according to Walker et al. [60]. The results of 2 earlier studies by Krantz et al. [61] on 17 patients treated with methadone and who developed TdP revealed that very high doses of methadone (mean 397 ± 283 mg/day) may be related to this arrhythmia. In addition, daily doses of this drug are associated with the prolongation of QT interval [61, 62]. Another study surveyed the effect of intravenous methadone alone and in combination with chlorobutanole on QT prolongation. Their data showed that the combination of 2 drugs causes QT interval prolongation and also showed a significant linear relationship between methadone log-dose and prolongation of QT [63]. A retrospective study on 167 patients receiving methadone indicated that even low doses of methadone can cause QT prolongation and TdP. The lowest dose in which TdP occurred was 40 mg/day. Also, a weak but significant dose-dependent effect on QTc length was observed [64]. Martell et al. [65] designed a prospective study on 160 patients. They demonstrated that oral methadone causes a modest QT prolongation, and also a positive correlation between methadone concentration and magnitude of QT interval was noted [65]. Correspondingly another study on 173 patients receiving methadone showed a positive relationship between methadone dose and QTc interval [35]. Fanoe et al. [34] who found no dose-dependent relationship between buprenorphine and QTc interval, as mentioned above, did find a significant correlation between QTc interval and methadone dose. Despite findings supporting the presence of a relation between methadone dose and QT interval prolongation, the evidence of some studies has not confirmed this. Recently Chowdhury et al. [66] reported a high prevalence of prolongation of QT interval in 291 patients on methadone, but the relationship between methadone dose and QTc was weak and not significant. Also they observed that the prevalence of ventricular arrhythmia was low in these patients [66]. Two separate studies also failed to find an association between methadone dose and QTc interval; however, Roy et al. [67] concluded that even low doses of methadone can produce significant prolonged QT interval, while Stallvik et al. [36] suggested that even modest doses of methadone (less than 100 mg/day) have no correlation with clinically significant QTc prolongation [36, 67]. In an analysis on 130 patients of whom 90 were receiving methadone for treatment of chronic pain, besides finding more evidence that methadone causes QT prolongation even in low doses (less than 80 mg/day), their results also showed there is no correlation between QTc interval magnitude and methadone dose, serum level and duration of use [68]. Several studies have specifically investigated the effect of methadone on QT interval in chronic pain patients. A retrospective study on 37 paediatric oncology patients who received methadone with a mean dose of 27 mg/day and mean duration of 49 days showed no association between methadone dose/duration and QT prolongation and they suggested that methadone is a safe drug in the paediatric population [69]. In another retrospective study on 1,246 patients who were older than 18 years and were receiving methadone for pain treatment, 49.4% had QTc prolongation, and this suggests that there is risk of QTc prolongation in pain management. They also showed this risk is higher in methadone doses of more than 100 mg/day [70]. The study of McNamara et al. [71] on 51 patients on

methadone, with a dose range of 5–180 mg/day, supported these findings and showed that even lower doses of methadone (5 mg/day) can cause QTc prolongation. This evidence was supported by a study in which 5% of patients on methadone (mean dose 18.2 mg/day) for pain treatment showed TdP [72]. On the other hand, a prospective study on 82 patients showed that in first month of initiating methadone, there was a prolongation in QT in comparison to the control group, but in the third and sixth months, no significant difference was seen [73]. Fredheim et al. [74] conducted an interesting study on patients with pain treated with morphine. They switched morphine to stable doses of methadone and they did not observe clinically or statistically significant QT interval changes [74].

Thus, one can infer that the risk of the QT interval prolongation and TdP even in low doses of methadone is likely. In addition, this risk may increase at high doses, long duration use, and utilization with some other drugs and especially in persons undergoing MMT.

Morphine and Hydromorphone

Morphine is a mu receptor agonist and is mostly used in treatment of acute, cancer- related and chronic pain [7]. Hydromorphone is another mu receptor agonist that is derived from morphine. Despite evidence of cardioprotective effects of morphine in animal studies [75–77], morphine and hydromorphone are related to various cardiac side effects such as histamine release, which leads to bradycardia, vasodilatation and hypotension, decreasing cardiac output especially when used in combination with benzodiazepines [7]. A few studies have reported the effect of morphine on QT interval and TdP. Fanoe et al. [78] failed to find any relationship between QT length and morphine (mean dose 120 mg, the dose range 30–300 mg). So did another more recent study that compared the effects of methadone and morphine on the heart rate, mean arterial pressure and QT interval; they did not find any association between morphine and QT interval, while methadone significantly increased QT interval. They also demonstrated that QT interval has a dose-dependent response to methadone [79]. According to another comparison study done by Wallner et al. [57], methadone was more often associated with QT interval prolongation than slow-releasing morphine and buprenorphine. In a case report, a patient with a history of depression was found unconscious because of overdosing on morphine, diazepam, citalopram, oxycodone and zopiclone at the same time and his initial ECG showed corrected QT interval of 650 ms. However, another study had shown that none of these drugs on their own affect QT interval [80, 81]. No relevant studies were found measuring effects of hydromorphone on QT interval. Thus, while data on morphine are scarce, a majority of evidence confirms its safety regarding heart electrical activity at least in routine doses.

Fentanyl

Fentanyl is a synthetic mu receptor agonist and is used before surgeries along with aesthetic drugs. Fentanyl has minimal effects on the cardiovascular system. Hypotension is a side effect of all opioids, but in comparison to other opioids, fentanyl is well tolerated. However, the use of fentanyl in combination with benzodiazepines may cause decreasing cardiac output and stroke volume [7]. Sufentanyl, remifentanil, alfentanil and carfentanil are analogs of fentanyl and are being used as sedatives before surgeries and as analgesics and have the same side effects as fentanyl [82]. Results on the effects of fentanyl and its analogs on QT are contradictory [83]. Chang et al. [84] demonstrated that at clinical doses (2 μg/kg), fentanyl not only does not prolong QT and QTc interval but also diminishes the prolongation of QT interval if used before laryngoscopy and tracheal intubation during propofol induction. Similarly, another study in 2013 showed that fentanyl does not prolong QT interval at a dose of 2 μg/kg before endotracheal intubation during propofol induction [85]. Interestingly, a case report even showed the shortening of QT interval after the use of fentanyl in a patient with congenital long QT syndrome [86]. Compatible with these findings, another study showed that fentanyl and remifentanil do not change QTc interval but that fentanyl failed to intercept increasing of QT and QTc interval dispersion after intubation, while remifentanil (0.25 μg/kg) successfully decreased QT interval dispersion. Thus, in conclusion, Cafiero et al. [87] suggested that while fentanyl is a safe opioid, remifentanil may be the choice of opioid treatment in patients at risk of dysrhythmias. By contrast, in 60 patients undergoing coronary artery bypass graft surgery, significant QT prolongation was observed after the injection of fentanyl (5 μg/kg) and vecuronium [88]. Also, in 2 recent studies, prolongation of QT interval was reported after treatment with fentanyl [16, 89]. Regarding alfentanil, there are 2 studies, all are old researches in patients during aesthetic induction, demonstrating that alfentanil has no effects on prolongation of QT interval. One report showed that pretreating patients with alfentanil has an attenuating effect on QT interval prolongation associated with laryngoscopy, but this effect was not observed in post-intubation QTc prolongation [90, 91]. No studies have been reported in humans to evaluate the effects of sufentanil on QT interval, but a case report showed QT interval prolongation after 24 μg/kg sufentanil, in a patient undergoing cardiac surgery [92]. However, an experimental study on guinea pig hearts showed that sufentanil has no effect on repolarization and another on canine purkinje fibres demonstrated significant lengthening of QT duration caused by high concentrations of sufentanil concentration [93, 94]. According to Kweon et al. [95], 1 μg/kg remifentanil not only does not prolong QT but also has preventive effects on QT prolongation following laryngoscopy and tracheal intubation. Remifentanil at smaller doses (0.25 μg/kg) has been shown to have attenuating effects after laryngeal mask placement [96]. Thus far, several studies on remifentanil demonstrated it is a safe opioid in high-risk patients before tracheal intubation and surgeries; in none of these studies remifentanil was found to have prolongation effect on QT interval [87, 97]. A study on animals yielded the same result; remifentanil was shown to have no effect on QT duration; however, it can depresses sinus node and most parameters of AV nodal function [98]. To date, there is no data showing effects of carfentanil on QT interval.

Overall, it seems that the effect of fentanyl and its analogs on QT interval is dose-dependent. In low doses, the probability of QT interval prolongation is less, but in high doses (5 μg/kg) this probability may increase. Nevertheless, there are no reports on the occurrence of arrhythmia following the use of these drugs.

Oxycodone

Oxycodone, a mu receptor agonist which is used as analgesic, does not have serious adverse effects on the heart but like other opioids can cause hypotension and bradycardia as well [7]. The first study that investigated the effects of oxycodone on QT interval

was by Fanoe et al. [78]. They designed a cross-sectional analysis of 100 patients with chronic non-malignant pain treated with morphine, tramadol, methadone and oxycodone. In addition to confirming the dose-dependent effect of methadone on QT interval, their result demonstrated that in higher doses (more than 100 mg) of oxycodone, the QT interval is longer [78]. Another recent report showed that overdose of oxycodone can cause QT prolongation. The median dose for patients with abnormal QT was 100 mg [99]. Also, a case report showed TdP in patients treated with a high dose of oxycodone after prolongation of QT interval. Due to oxycodone consumption, Taku-Tsubo cardiomyopathy augmented the prolongation of QT followed by TdP [100]. However, more research needs to be done to confirm these results.

Tramadol

Tramadol is widely used for treatment of pain and is a weak synthetic mu receptor agonist. Tramadol overdose can cause nausea and vomiting, hypertension, tachycardia, depression of central nervous system and respiratory system, agitation and seizure. In analgesic doses, cardiovascular side effects are not of much concern; however, serotonin syndrome might occur due to the action of tramadol as a serotonin and norepinephrine reuptake inhibitor, which can lead to cardiac arrhythmia [7, 101, 102]. The effect of tramadol in QT interval was first evaluated by Emamhadi et al. [103] in 479 patients, one fourth of them had QTc prolongation, thereby suggesting a probable potassium channel blockade effect. According to this report, tramadol might pose a risk for QT interval prolongation. In addition, a recent study showed a significant increasing in QT interval after treatment with tramadol [16]. Further evaluation needs to reach a proper conclusion.

Other Opioids

Meperidine or pethidine is a mu receptor agonist and its consumption is decreased because of its serious side effects such as decreasing myocardial contractility, blood pressure and cardiac output following intravenous administration and CNS toxicity in chronic oral use [7]. A recent study on 58 patients who received meperidine at a dose of 304 ± 133 revealed that it causes QTc-interval prolongation in correlating with normeperidine plasma concentration [104]. Also, a case report in 2011 presented a 16-year old boy without any underlying cardiac disease who developed ventricular tachycardia, ventricular fibrillation and QT interval prolongation over 500 ms following intravenous injection of meperidine for pain control before colonoscopy [105]. Levorphanol is a mu, delta, kappa1, kappa3 agonist and N-methyl-D-aspartate receptor antagonist. Levorphanol also acts as a serotonin and norepinephrine reuptake inhibitor and is indicated as an analgesic in patients who do not respond to other opioids [106, 107]. Similar to other mu receptor agonists, levorphanol has some adverse effects such as nausea and vomit, flushing, constipation and so on [107]. Levorphanol is as effective as methadone with a difference that has less serious side effects like QT interval prolongation; thus, according to several studies, levorphanol is a safe opioid that should be considered more in clinical pharmacotherapy [107–109]. LAAM is another synthetic mu receptor agonist being used in OMT. Although it is even more effective than methadone in heroin maintenance treatment, it may soon be withdrawn from the market because of some reports of life-threatening cardiac arrhythmia related to LAAM, and also because it has an association with QT interval prolongation [110, 111]. There are several cases in which QT interval prolongation and TdP was reported and in one of them TdP developed after treating with high doses of LAAM (3 mg/kg/dose) and also there was interaction with flouxetin, which is known to have the property of prolonging QT interval [112]. As mentioned above, Wedam et al. [30] for the first time evaluated the effects of LAAM on QT interval in a double-blind clinical trial in which 55 patients received BMT, 55 patients received MMT and 55 patients received LAAM and the QTc was compared between 3 groups and they demonstrated that methadone and LAAM are associated with significant mean QTc interval prolongation more than 30 ms [30]. Two years later, another clinical trial was designed by Wieneke et al. [113] to investigate the effects of LAAM on QT interval. In this study, 31 patients were treated with LAAM and 22 patients were on methadone. According to the result, QTc prolongation is more likely in patients with LAAM and happens to a higher degree than methadone. The interesting finding of this research was that shifting from methadone to LAAM treatment caused an increment in the mean QT interval compared to patients permanently on methadone [113].

Codeine, Loperamide, Tapentadol,
Oxymorphone, Hydrocodone

Codeine or 3-methylmorphine is another mu receptor agonist opioid used to treat mild to moderate pain, diarrhoea and cough. Its common side effects are drowsiness and constipation like other opioids [8, 114, 115]. There is no in vivo study to evaluate effects of codeine on QT interval but 2 in vitro studies agree that codeine does not have the potential to block the hERG K^+ channel, which is the main mechanism of prolongation of QT [20, 116]. Recently, a case report demonstrated the arrhythmogenic effect of over-dose (400 mg daily) of loperamide, a μ-opioid-receptor agonist, as QTc prolongation and ventricular tachycardia in an opioid abuse [117]. Our research did not find any study that has evaluated the connection between tapentadol (mu receptor agonist), oxymorphone (semisynthetic mu receptor agonist) and hydrocodone (semisynthetic mu receptor agonist) [7] and QT interval, and this needs to be addressed in the future.

Opium

Opium is derived from a plant called Papaver somniferum L., and contains eighty different alkaloid ingredients such as morphine and codeine and thus has an analgesic effect. Although it has been established that opium does not decrease blood pressure, serum lipids and blood glucose, it is being extensively abused and it is because of this wrong traditional belief that its outcome, opium-dependence, is a major public health problem in some parts of the world especially in Asia and the Middle-East [118–122]. In an animal study, Najafipour and Joukar investigated the long-term and short-term effects of opium smoking in association with hypercholesterolemic diet on cardiac arrhythmias. They showed that opium smoking along with hypercholesterolemia significantly increased the incidence of fatal arrhythmia. This effect was not mediated by changes in the QT interval [118]. To our knowledge, there are no studies in humans on the effect of opium on QT interval.

Atrial Fibrillation and Post-Myocardial Infarction Arrhythmia

Atrial fibrillation (AF), a common cardiac arrhythmia, is a serious consequence post coronary artery bypass grafting and post myocardial infarction (MI) [123]. In few recent studies, a

relation between opioids and AF has been shown. The Reasons for Geographic and Racial Differences in Stroke study explained the association between opioid use and increasing AF prevalence. Most common opioids that were used in this study were hydrocodone, propoxyphene and tramadol [124]. A large study in 2016 investigated the association of morphine and incidence of AF in breast cancer patients in Taiwan by comparing AF incidence in patients treated and not-treated with morphine as an analgesic. Among 73,917 patients included in this study, 18,671 patients received morphine and 55,246 were not treated with morphine. The results indicated a greater and significant risk of AF incidence in patients treated with morphine [125]. However, an earlier study in 2008, which was done on decompensated heart failure patients, did not indicate any significant difference in prevalence of AF in patients who received morphine and those who did not receive morphine [126]. Opium, a mixture of several opioids like morphine and codeine, is associated with AF as well, according to a few other studies. In a retrospective study conducted by Sabzi et al. [127] on 670 patients undergoing coronary artery bypass grafting, opium consumption was associated with post-operative AF and was introduced as a new predictor of AF incidence in these patients [127]. Correspondingly, Mirzaiepour et al. [128] confirmed these results in a report on a patient after MI. They concluded that patients consuming opium are at higher risk of sinus bradycardia, sinus tachycardia and AF. Other post-MI arrhythmia like PVC, premature atrial contraction, complete heart block and paroxysmal supraventricular tachycardia were more prevalent in opium-consuming patients as well. However, there was no difference between 2 groups concerning of ventricular tachycardia incident. They also established that patients with a higher prevalence of post-MI arrhythmia had a longer duration of opium usage [128]. An earlier study reported the increase of sinus tachycardia, ventricular extrasystole, supraventricular extrasystole with infrequent paroxysms of supraventricular tachycardia in patients with opium and ephedrone abuse [129].

Discussion

Despite the inadequacy and contradictory nature of some studies, accessible reports show that some opioids especially LAAM and methadone are associated with cardiac electrical disturbance. These drugs predispose to of QT interval prolongation and TdP occurrence even in low doses. Severity of risk increases when they are consumed in higher doses, for long periods and along with other interacting drugs. Some opioids such as fentanyl, tramadol and oxycodone have intermediate risk. They usually produce a long QT interval and occasionally arrhythmia in high doses. Others such as morphine and buprenorphine are low-risk and in routine doses they seldom create a long QT interval and arrhythmia. Despite the limited data, it seems that in patients with coronary heart diseases the chronic use of opium, morphine, tramadol, hydrocodone, propoxyphene and codeine may increase the risk of PVC, AF, and other atrial arrhythmia. Research has shown that there is a similarity in the chemical structure of some synthetic opioids such as LAAM, methadone and d- propoxyphene. They have biphenyl moieties similar to some antihistamine drugs that prolong QT interval. However, biphenyl rings are not sufficient for blocking of hERG channel because methadone metabolite 2-Ethylidene-1,5-dimethyl 3,3-diphenylpyrrolidine, despite the presence of biphenyl rings, cannot significantly inhibit the hERG current. Many attempts have been made to elucidate a relationship between the structure and function for hERG blockers. Despite the many advances, hERG blockers have a lot of structural variation and there is still no clear relationship between the structure and activity of these drugs [12].

It is obvious that underlying diseases like renal and hepatic failure may be associated with enhanced plasma concentrations of opioids and increase the risk of the QT interval prolongation and arrhythmia. To reduce the risk of arrhythmia, high doses of these medications must be used cautiously. In addition, combinations of opioids especially methadone with other medications that inhibit cytochrome P450 enzymes may increase the risk of QT prolongation [21]. Also co-administration of opioids with other drugs, which prolong the QT interval and increase the risk of QT prolongation-associated arrhythmias such as class I (Quinidine, Procainamide, Disopyramide and etc.) or III (Amiodarone, Dofetilide, Ibutilide, Sotalol and etc.) antiarrhythmic agents, calcium channel blocking agents (Bepridil), some antidepressants agents (maprotiline, nortriptyline, Imipramine, Desipramine, clomipramine, trimipramine and etc.), some antibiotics (Pentamidine, Clarithromycin, Halofantrine, Sparfoxacin, and etc.) and some antipsychotic agents (Chlorpromazine, Droperidol, Haloperidol, Mesoridazine, Pimozide, Thioridazine and etc.) [21, 130, 131], should be used with caution. Moreover, from the perspective of opioid substitution, other issues such as the potency of the drug, its availability and patient preference are important and can affect physician prescription [132]. For example, studies and clinical experience revealed that users have more satisfaction with methadone than buprenorphine, and buprenorphine prescriptions have failed to overtake methadone in the United Kingdom [133]. The higher effectiveness of methadone over buprenorphine may stem from the fact that methadone is a long-acting mu opioid receptor; however buprenorphine has partial agonist activity on mu opioid receptor and at a low dose may be insufficient to satisfy the withdrawal symptoms and cravings,

especially if the addict is used to very high doses of heroin [134]. This in turn increases the tendency of patients to methadone and may enhance the risk of cardiac arrhythmia.

Conclusion

The arrhythmogenicity of opioids is different. Although it is accepted by patients, methadone has a greater risk of arrhythmias. Some of them including tramadol and oxycodone have intermediate risk and some other opioids such as morphine and buprenorphine are low-risk drugs. Opium consumers are at risk of supra-ventricular arrhythmias, bradycardia, cardiac block and AF. To reduce arrhythmogenic risk, high doses of opioids must be used cautiously with periodic monitoring of ECG in high-risk consumers such as patients under OMT.

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Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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