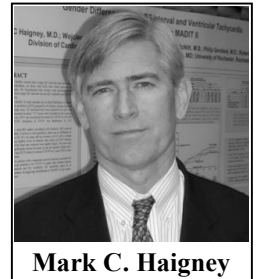


# The Impact of Opioids on Cardiac Electrophysiology

Erich F. Wedam and Mark C. Haigney\*

Division of Cardiology, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland and Division of Cardiology, Department of Medicine, Walter Reed National Military Medical Center, USA

**Abstract:** Synthetic opioid agents have been used in modern medicine for over a century and for opioid addiction treatment for over a half-century. Liberal use of opioids in the United States has been attended by an extraordinary increase in opioid-related mortality, with over 16,000 deaths in 2012. As there have been advances in opioid agents for pain and addiction, so have there been advances in our understanding of the cardiac effects of these agents. In the last 10 years, significant data regarding electrophysiologic effects of these agents have been collected. We aim in this review to discuss the effects on cardiac electrophysiology of the various opioid agents currently in use and the evidence that these effects are contributing to the rise in opioid-related mortality.



**Keywords:** hERG, opioid, QT, sudden death, torsades.

## INTRODUCTION

Opium and its derivatives have been used for millennia. The Sumerians are documented to have used an extract of opium for religious rituals in the third millennium B.C. and documents as early 1500 BC indicate opium use for medicinal purposes [1]. Although morphine and codeine were not isolated until the early 19<sup>th</sup> Century, the dangers of these agents prompted the search for safer and less addictive alternatives. The first of these alternatives, heroin, was introduced in 1898 [1] and since then a number of new opioid agonist, antagonist and mixed agonist/antagonist agents have been developed. Although beyond the scope of this review, Cambell and Novell provide a fascinating overview on the development of opioid alternatives in the 20th century.

In the last two decades, the potential for non-cardiac pharmacologic agents to produce cardiac effects has been better recognized. In 1990, Monahan *et al.* reported the discomfiting finding that a widely used non-sedating antihistamine, terfenadine (Seldane), was capable of prolonging cardiac electrical activity and causing life-threatening ventricular arrhythmia [2]. From that time, the FDA has required that all newly developed drugs be assessed for their potential cardiac effects prior to their approval. A number of opioid agents had been in regular use for decades prior to the recognition of these possible effects and the change in FDA scrutiny. Nevertheless, a body of evidence has developed suggesting that opioid agents have variable degrees of cardiac effects. The scope of these cardiac effects will be reviewed here.

\*Address correspondence to this author at the Division of Cardiology, Department of Medicine, Uniformed Services University of the Health Sciences, A3060, USUHS, 4301 Jones Bridge Road, Bethesda, MD 20814, USA; Tel: 301-295-3826; Fax: 301-295-3557; E-mail: [mhaigney@usuhs.edu](mailto:mhaigney@usuhs.edu)

## CARDIAC ELECTROPHYSIOLOGY

From the standpoint of electrophysiology, the heart contains three types of cells: nodal, or “pacemaker cells”, contracting muscle cells, or “myocytes,” and Purkinje cells. The three cell types exhibit significant differences in structure and function, with nodal and Purkinje cells acting to initiate and conduct electrical activity to the myocytes. There are few data beyond case reports to suggest that opiates have any direct effect on the electrical behavior of nodal or Purkinje cells, but substantial evidence of impact on the myocytes.

Myocytes represent the vast mass of cardiac tissue, and perform the mechanical work of the heart. The electrical activity of the cardiac myocyte and its coupling with mechanical action are central to fundamental cardiac function. During the cardiac cycle, an individual myocyte exhibits a nearly 100 mV change in electrical voltage from negative to positive during systole (“depolarization”) and then positive to negative during diastole (“repolarization”). The time course of this voltage change describes a characteristic shape represented by the “action potential” (Fig. 1a) and is brought about by the transmembrane movement of certain critical ions, predominantly sodium during depolarization and potassium in repolarization. These ions flow through specific pore-forming proteins (or “channels”) in the myocyte membrane. Collectively, the aggregate action potentials produce the characteristic tracings of a surface electrocardiogram, and the total duration of ventricular depolarization and repolarization is represented by the QT interval (Fig. 1b). The impairment of movement of any one of these electrolytes can have global effects on this electrical process. Drugs and toxins may lodge in these channels and either increase or decrease ionic flow during the action potential, altering its shape and changing the appearance of the surface electrocardiogram. The most common channel to be affected by drugs

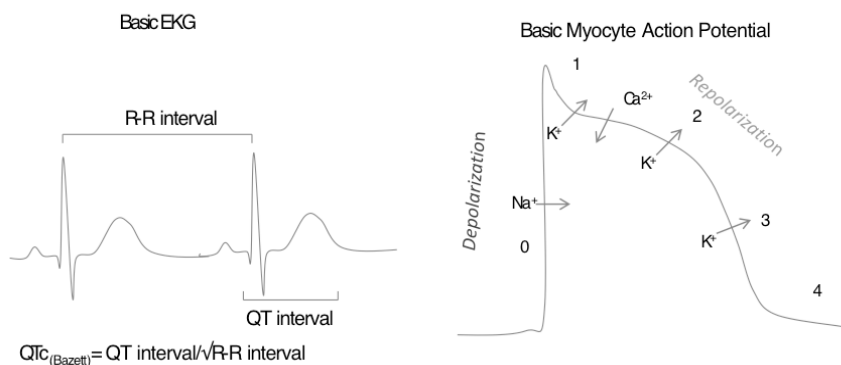


Figure 1b

Figure 1a

**Fig. (1).** Comparison of the ventricular action potential and the surface electrocardiogram.

is the rapid component of the delayed rectifier potassium channel. This conductance is referred to as  $I_{K_r}$ , and the protein associated with  $I_{K_r}$  is the human ether a-go-go related-gene channel ( $I_{HERG}$ ). Potassium flow through this channel is critical for returning the voltage of the heart cell to its diastolic potential during “repolarization.” While other channels also participate in repolarization, the hERG-related channel is the most important for determining the action potential duration, and hence the QT interval, in the resting state. Unfortunately, the structure of the channel is such that many drugs are capable (to varying degrees) of lodging in its central pore and obstructing flow of potassium. The effect of decreased flow through this channel is prolongation of the duration of the action potential and consequently prolongation of the QT interval [3]. In the treatment of cardiac arrhythmias, the duration of the action potential may be intentionally prolonged with medications (i.e. sotalol or dofetilide) intended to block current flow through the hERG channel to achieve arrhythmia suppression. Unfortunately, the drug-induced prolongation of repolarization can inadvertently increase the heterogeneity of electrical state between adjacent regions of cardiac muscle, promote spontaneous, abnormal depolarizations, and actually increase the risk for arrhythmia. The arrhythmia most commonly induced by drugs prolonging repolarization and the QT interval is a type of polymorphic ventricular tachycardia known as Torsades de Pointes (TdP) [3].

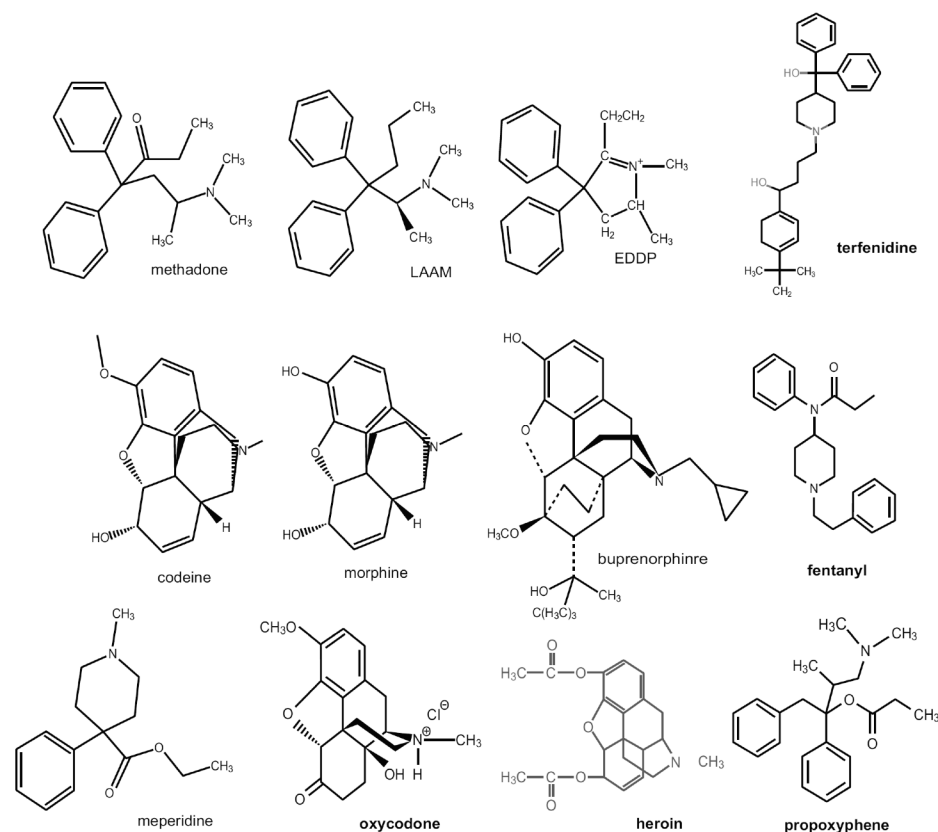
The occurrence of TdP is a rare event, and in order to reduce the size of clinical trials investigating the safety of drugs and identify potentially arrhythmogenic compounds, measurement of the QT interval is used as a surrogate endpoint. Currently, the FDA considers several findings on electrocardiogram clinically significant for the risk of cardiac arrhythmia, with greater magnitudes of QT prolongation generating greater concern.

Due to the complex interaction of changing extracellular and intracellular ion concentrations with ion channel biophysics, the QT interval shortens at higher heart rates in healthy individuals. In order to compare values of QT taken at different heart rates, an attempt is made to normalize or “correct” the value to a heart rate of 60 beats per minute. Typically the QT is divided by the square (“Bazett correction”) or cube root (“Fridericia correction”) of the inter-beat interval, although an array of alternative approaches have

been tried. (The commonly-applied Bazett correction introduces error at heart rates above 80 beats per minute, resulting in healthy individuals being labeled as having long QT intervals, and the Fridericia approach preferred.) The result is expressed as the heart rate corrected QT or “QTc.” An increase in the group mean QTc of >20 msec is considered a definitive sign of TdP risk. Because TdP tends to occur in “outliers,” particular attention is paid to individuals manifesting an absolute increase in QTc > 60 msec from baseline or a peak QTc > 500 msec, as these individuals have a risk of TdP of 3% or greater [4]. A number of non-cardiac agents have effects on this  $I_{K_r}$ / $I_{HERG}$  channel with variable effects on cardiac repolarization and variable potential for cardiac arrhythmia [5]. As many authors have pointed out, however, the QTc is an imperfect marker of arrhythmic risk, lacking specificity and, to a much lesser degree, sensitivity. The development of better surrogate measures is an area of considerable interest to investigators, regulators, and the pharmaceutical industry.

## OPIOID PHARMACOLOGIC ACTION

The understanding of opioid action on the central nervous system began to evolve in the early to mid 1970s. Several authors demonstrated that there were binding sites within the central nervous system that were stereo-specific for opiates and that there was in fact endogenous opiate production [6-9]. The presence of the different types of opioid receptors ( $\kappa$ ,  $\delta$  and  $\mu$ ) had been demonstrated not only in the central nervous system but in the gastrointestinal tract, reproductive tract and peripheral nervous system [10, 11]. The various opioid receptors share a common affinity for the specific chemical structure found in opioid agents, namely an amine ( $N(CH_3)_x$ ) structure in close proximity to an aromatic ring (Fig. 2) [1]. Interestingly, some of these opioid receptors had been shown to activate inward rectifier potassium channels and inhibit voltage dependent calcium channels [12, 13]. Nevertheless, concern regarding potential cardiac action of opioid agents first came to light in 2001 when Deamer *et al.* published a case series of TdP associated with high dose levomethadyl acetate (ORLAAM) [14]. In 2002, Krantz *et al.* published a case series of seventeen individuals with methadone-associated TdP. These revelations prompted others to investigate opioids and their potential effect on hERG cardiac channel function. Katchman *et al.* investigated



**Fig. (2).** Molecular structures of common opioids compared to terfenadine, a potent hERG channel blocker.

the effect of several opioid agonists on  $I_{kr}/I_{HERG}$  in a cell culture model expressing human hERG-related channels. These investigators found that levomethadyl acetate and methadone were potent inhibitors of this channel, manifesting a 50% reduction in current in the low micromolar range which represent achievable plasma concentrations, while other opioid agonists such as morphine and codeine block the channel at concentrations that are orders of magnitude above likely serum levels (Table 1) [15]. Interestingly, Zünkler and Wos-Maganga demonstrated that heroin is 100-fold less potent than methadone in  $I_{kr}/I_{HERG}$  inhibition as demonstrated in a similar cell culture model, a difference in potency which is comparable to that of morphine and codeine [16]. Fanoie *et al.* evaluated the effects of oxycodone on  $I_{kr}/I_{HERG}$  in two types of cultured cell lines. In this single report, oxycodone showed weak inhibitory effects at very high concentrations (50% inhibition at 171  $\mu\text{M}$ ) in one heterologous cell line but no effect in a second [17]. These compounds share the amine and aromatic structure configuration associated with opiate receptor agonism, however their structures are clearly distinct from potent hERG-blocking agents. Levomethadyl acetate and methadone have a biphenyl structure similar to terfenadine but unlike other opioids (Fig. 2) [15]. In this same study, EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) a metabolite of methadone which has this biphenyl structure did not demonstrate the same degree of channel inhibition. The authors suggested that the attenuated  $I_{kr}/I_{HERG}$  inhibition is likely due to the presence of a pyrrolidine ring in which the amine structure is positively charged [15]. In a more recent publication, Kang *et al.* showed that LAAM specifically inhibited

$I_{kr}/I_{HERG}$  and not other forms of cardiac  $\text{K}^+$  channels [18]. Oxycodone does not share this biphenyl structure, and specific explanation for the (albeit equivocal) evidence of low-potency  $I_{kr}/I_{HERG}$  blockade is not clear [17]. Based on the *in vitro* evidence of the potential for hERG blockade, retrospective and prospective assessments of the clinical cardiac effects of opioid agents have since been conducted in a number of patient populations.

### LEVOMETHADYL ACETATE (LAAM)

As noted above, LAAM was the first opioid agent to be identified as having clinically concerning cardiac effects [14]. Although methadyl acetate had been shown in numerous studies over a quarter century to be quite effective in treating opioid addiction [19-27], the United States Food and Drug Administration (US FDA) and the European Agency for the Evaluation of Medicinal Products issued warnings regarding LAAM and the potential for adverse cardiac effects [28, 29]. Aside from the significant case report of TdP [13], there have only been two additional studies assessing the electrocardiographic effects of LAAM [30, 31]. In these studies, the mean QTc increase ranged between 9 and 30 msec with similar doses of LAAM used (75-115 mg, given three times per week). In a blinded, randomized analysis, the mean QTc increased  $27 \pm 5$  msec at 4 weeks ( $p < 0.001$ ) and an additional  $22 \pm 5$  msec over the remaining 12 weeks. Five of 46 subjects exhibited a peak QTc  $> 500$  msec at some point in the study [30]. In 2003, Roxane Laboratories withdrew the compound in the US, and further assessment of LAAM has been curtailed due to its limited availability.

**Table 1. Comparison of the relative potency of selected opioids for inhibiting the hERG channel.**

Drug	IC <sub>50</sub> for hERG Block	Max. Plasma Concentration (C <sub>max</sub> )	Ratio IC <sub>50</sub> /C <sub>max</sub>
LAAM	2.2 μM	1 μM	2.2
Methadone	9.8 μM	3.6 μM	2.7
EDDP	>50 μM	1 μM	>50
Meperidine	75 μM	1.3 μM	58
Fentanyl	1.8 μM	30 nM	60
Buprenorphine	7.5 μM	36 nM	208
Morphine	>1 mM	2.5 μM	>400
Codeine	>300 μM	0.66 μM	>455
Heroin	427 μM	10-13 μM	34-43

Ref. [15, 16].

## METHADONE

Bockmühl and Ehrhart synthesized methadone (2-dimethylamino-4,4-diphenylheptanon-(5)) for Hoechst pharmaceuticals in 1939 and this agent was introduced to the US market by Eli-Lilly in 1947 [32]. Available as an analgesic from that point on, the use of methadone as a therapy for opioid addiction was not first reported until 1965 by Dole and Nyswander [33, 34]. Concerning reports of adverse cardiac events related to methadone use first surfaced in 1996 with a report of TdP to the FDA MedWatch program [35]. In 2005, Pearson and Woosley reported that between 1969 and 2002 there were 43 cases of TdP and 16 cases of QT or QTc prolongation associated with methadone use with only 3 of the cases reported prior to 2000 [35]. Poluzzi *et al.* discovered that there were 83 cases of TdP associated with methadone use reported to the FDA Adverse Event Reporting System (AERS) between 2004 and 2007 [36]. In 2002, Krantz *et al.* were the first to report a case series of TdP associated with high dose methadone (mean dose 397±283mg) and in this cohort found a mean QTc of 615±77msec. In this series, methadone dose was significantly associated with TdP and QTc prolongation [37, 38]. A literature review conducted by Justo *et al.* in 2006, found 14 reports of TdP with a total of 40 patients treated with high dose methadone (mean dose 231± 201mg, range 60-1000 mg/day) for opioid dependence. The most common risk factor for TdP was a daily dose of methadone in excess of 60 mg. The mean QTc for the patients in this particular review was 598±75 msec [39]. A PubMed search for methadone and TdP yields over 36 case reports or case series of documented TdP in patients treated with I.V. or oral preparations of methadone. [Search terms: Torsades de Pointes AND methadone] In the last 10 years, there have been numerous reports assessing the effects of methadone on the QT interval. In these reports, the incidence of QTc >500, a level widely believed to confer high risk for TdP, ranges between 1% and 16%. In most reports, cases of significant prolongation were dose dependent [29, 38, 40-65]. There have been few prospective analyses that have demonstrated the relationship between methadone and pro-

longation of the QT interval. The first of these prospective studies was an open-label study conducted by Martel *et al.* involving 160 patients on methadone maintenance therapy with median daily doses of 80-90 mg (range 20-200mg). Baseline EKGs were performed and at 6 and 12 months into therapy. The mean QTc interval at follow-up was 430.8 ± 24 msec at 6 months and 431.5±26 msec at 12 months. The mean increase in the QTc from baseline was 12.4±23 msec ( $p<0.001$ ) at 6 months and 10.7±30 ( $p=0.001$ ) msec at 12 months and there were 2 (1.8%) patients exhibiting a peak QTc >500 msec. In both univariate and multivariate analyses, methadone dose was significantly associated with QTc prolongation [40, 41]. As referred to previously, a double-blinded, randomized trial assessing the clinical efficacy of LAAM, low dose (20mg) and therapeutic (60-100mg) methadone and buprenorphine involved prospective assessment of EKG data. In this trial, the therapeutic methadone treated patients demonstrated an in-group mean increase in QTc of 17.3±5 msec at four ( $p=0.003$ ) and an additional 17±5 msec at 16 weeks. Of these patients, 23% manifested a QTc >470 msec for males or 490 msec for females ( $p<0.001$ ), 12% had an increase in QTc of >60msec from baseline [odds ratio compared to buprenorphine, 8.4; 95% CI, 1.9-36.4] and six of 52 subjects manifested a QTc >500msec ( $p>0.001$ ) [30]. Not all investigators have found a tendency for methadone to prolong the QTc. A prospective, open label assessment of QTc in advanced cancer patients treated with methadone over an 8 week period conducted by Reddy *et al.* produced results showing the mean QTc interval shortened by 50 msec, an effect, if genuine, which would be expected to be very pro-arrhythmic [42, 43].

Most recently, Stallvik *et al.* conducted a prospective assessment of QT interval effects of methadone over 6 months. In this study patients underwent full detoxification and controls for illicit drugs or other medications that might influence methadone metabolism or affect QTc were put into effect. The mean dose of methadone was 88.2 ±15.3 mg/d at 1 month and 95.5±16.2 mg/d at 6 months. The mean QTc at baseline was 406±19.1 msec and the QTc measured at fol-

low-up was  $409 \pm 19.5$  msec and  $408 \pm 18.0$  msec at 1 and 6 months respectively. The authors found no QTc prolongation at the doses studied with no significant correlation between measured serum methadone concentration and QTc. They conclude that doses of methadone less than 100 mg per day do not prolong the QTc, contrary to the findings of Wedam *et al.* [65]. In light of the numerous other reports finding QTc prolongation at these methadone doses, the *in vitro* evidence of hERG blockade by methadone, the results of these latter two studies are difficult to explain. It should be noted, however, that a rigorous evaluation of a drug's effect on the QT interval requires both that all investigators be blinded to treatment assignment and that the study demonstrate sensitivity by using a positive control. If a study fails to find evidence of QT prolongation, the results are only believable if the investigators can demonstrate that they can detect QT prolongation using an agent with a small but proven effect. Typically, regulatory agencies require the use of a positive control such as the fluoroquinolone moxifloxacin to prove that the sponsors can detect small but significant QT prolongation in a blinded, randomized analysis. Omitting such a comparison risks biasing the study in favor of finding no QT prolongation, an outcome that is highly desirable for the sponsor. To date, only our 2007 study in fulfills the requirements of being double blinded, randomized, and containing both positive (LAAM) and negative (buprenorphine) controls.

There have been several epidemiologic studies reporting an increased incidence of death associated with methadone [66-70]. Increasing use has been associated with a sevenfold increase in methadone poisoning deaths within the United States between 1999 and 2006, yet the increased mortality is out of proportion to the use [66]. Paulozzi and Ryan noted that 22% of all opioid related mortality in 2002 was due to methadone despite it only constituting 6% of the morphine-equivalents distributed [67]. Chugh *et al.* prospectively assessed the records of sudden death in the greater metropolitan area of Portland, Oregon between 2002 and 2006. In this study, 72 of 177 consecutive fatalities were found to have evidence of methadone on toxicology examination, while only 12 of 177 subjects had other opioids detected. 43 of the 77 were excluded from further analysis if their methadone level was greater than 1.0 mg/L (n=11) or evidence of recreational drug use/overdose was present (n=32). Of the remaining 29, there were 22 who had undergone a "detailed" autopsy. Five of these subjects were identified as having a structural cardiac abnormality that might constitute a cause of sudden death (23%), while in the remaining 17 no specific cardiac abnormality could be identified. This group was compared to the 106 autopsied subjects without methadone. In this second group, 60% of the patient's had a cardiac structural abnormality to account for the cause of sudden death, versus 23% of the methadone subjects, a highly significant difference (p=0.002, Pearson chi-square) [68]. The authors concluded: "The low prevalence of identifiable cardiac disease or structural abnormalities in the cases with therapeutic levels of methadone (<1 mg/L) strongly suggests a causative role for methadone in the pathogenesis of sudden cardiac death among this group". Sudden death related to cardiac arrhythmia leaves no characteristic pathologic findings, so definitive association between methadone and ar-

rhythmic death is difficult. Alternatively, death due to respiratory depression cannot be ruled out, although the low prevalence of other opioids that also suppress respiration in the sudden death group argues that a unique property of methadone is responsible.

Other retrospective studies of methadone associated deaths show a complex picture. Vormfelde and Poser and Heinemann *et al.* separately demonstrated that upwards of 65-70% of the methadone related deaths occurred in individuals without a history of methadone maintenance therapy (MMT) [69, 70]. In individuals with a history of MMT, 51% of the methadone related deaths occurred in the dose adjustment period [69]. This latter observation had been made earlier by Capelhorn in 1998 noting that there is an increased mortality within the first 2 weeks of methadone therapy [71]. As this collection of studies illustrates, multiple factors are at play with respect to mortality associated with methadone. Prior studies have shown that the efficacy of MMT is related significantly to the rate of change in methadone concentration and specifically the enantiomer of methadone (i.e. (R)- and (S)-methadone) more than the absolute concentration at a given point in time [72-79]. Eap *et al.* and Foster *et al.* have shown that there is significant inter-individual variability in the clearance, volume of distribution and protein binding of the enantiomers of methadone [75, 76]. Eap *et al.* showed that differences in metabolism between patients can result in seven-fold differences in enantiomer concentrations [77]. Eap *et al.* also showed that, between patients, there can be a 17-fold difference in the trough concentration of (R)-methadone measured and the dose of racemic (R/S) methadone given [78]. Ower *et al.* published a case illustrating significant QT interval variation within a patient on a stable dose of racemic methadone for chronic pain [48]. It is notable that Eap *et al.* showed that (S)-methadone is 3.5 times more potent than (R)-methadone in blocking  $I_{kr}/I_{HERG}$  [79]. Lin *et al.* corroborated these findings independently [80]. Eap *et al.* also showed that individuals with cytochrome P450 CYP2B6 slow metabolism had higher S-methadone plasma concentrations and demonstrated longer mean QTc than extensive metabolizers. S-methadone is apparently preferentially metabolized by CYP2B6 and it is estimated that 6% of Caucasians and African-Americans are CYP2B6 slow metabolizers [79]. Skjervold *et al.* conducted a retrospective assessment of QTc in patients and attempted to correlate these measurements with (R)- and (S)- methadone serum concentrations. In contrast to the findings of Eap *et al.*, they found that QTc prolongation weakly correlated more with a higher (R)-methadone concentration [81]. Fonseca *et al.* also assessed QTc in 109 patients and noted significant prolongation but did not demonstrate significant correlations between (R)- or (S)- methadone concentrations [55]. Ansermot *et al.* in 2010 prospectively found that the QTc significantly reduced when (R)-methadone was substituted for racemic methadone and the opposite occurred when racemic methadone was substituted for (R)-methadone [82]. Although methadone is predominantly metabolized by the cytochrome P450 CYP3A4 and in addition to CYP2B6, the enzymes CYP1A2, CYP2D6, 2D8, and 2C8/2C9 are also involved and competition with numerous other drugs (Table 2) can affect methadone serum concentrations and end-organ effect. Additionally, methadone is over 80% protein bound in the

**Table 2. Common inhibitors of CYP [57].**

Inhibitors of CYP2D6	Inhibitors of CYP3A4	
Amiodarone	Amiodarone	Itraconazole
Bupropion	Amprenavir	Ketoconazole
Chlorpheniramine	Aprepitant	Lapatinib
Chloroquine	Atazanavir	Miconazole
Chlorpromazine	Barbiturates	Nefazodone
Cinacalcet	Chloramphenicol	Nelfinavir
Diphenhydramine	Clarithromycin	Phenytoin
Duloxetine	Conivaptan	Posaconazole
Fluoxetine	Cyclosporine	Rifampin
Halofantrine	Darunavir	Ritonavir
Haloperidol	Dasatinib	Quinupristin
Imatinib	Delavirdine	Saquinavir
Paroxetine	Diltiazem	Tamoxifen
Perphenazine	Erythromycin	Telithromycin
Propafenone	Fluconazole	Troleandomycin
Propoxyphene	Fluoxetine	Verapamil
Quinacrine	Fluvoxamine	Voriconazole
Quinidine	Fosamprenavir	
Quinine	Glucocorticoids	
Terbinafine	Naringenin (Grapefruit)	
	Imatinib	
	Indinavir	
	Isoniazid	

serum, mostly to  $\alpha$ 1-acid glycoprotein. Nutritional status, inflammatory state and other co-morbidities can affect protein binding [83]. P-glycoprotein (ABCB1) is apparently important to the pharmacokinetics and dynamics of methadone particularly with respect to drug-drug interactions [84]. Anchersen *et al.* recently demonstrated the potential contribution of latent genetic predisposition, namely Long QT syndrome (LQTS), as another factor in the noted prolongation of QT associated with methadone but more interestingly noted the wide variation in QT interval measurements over time even among those patients with known LQTS. In their analysis 2 of 200 were heterozygous for LQTS [60]. The prevalence of LQTS in the population has been estimated between 0.01% and 1% and may in fact be underestimated with the currently available data [85].

A particular drug-drug interaction commonly cited regarding methadone is that with benzodiazepines. Kuryshev *et al.* showed that diazepam alone did not affect myocyte action potential duration but in combination with methadone was synergistic in prolonging the action potential over and above that of methadone alone [86]. Commonly, respiratory depression is cited as cause for mortality when methadone and benzodiazepines are used in combination; however, Lintzeris *et al.* have shown that a combination of methadone and diazepam resulted in no difference in oxygen saturation in patients compared with methadone alone [87, 88]. Respi-

ratory depression is a particularly important consideration especially with regards to sleep disordered breathing and sleep apnea. Central sleep apnea is more prevalent in MMT patients than non-MMT patients and in some patients is related to methadone blood concentration yet other factors are involved [89]. Prior studies have demonstrated that significant QT interval prolongation and bradycardia are associated with sleep apnea and that sleep disordered breathing, namely obstructive sleep apnea, is associated with a 17.5 fold increased risk for ventricular arrhythmia [90, 91]. Schwartz *et al.* demonstrated that nearly 50% of patients with Long QT syndrome type 2 (LQT2), who have a reduced  $I_{kr} / I_{HERG}$  channel activity, have lethal cardiac events during sleep [92]. Clearly, the metabolism of methadone is quite complex and is influenced by several factors which contribute to its intrinsic cardiac electrophysiologic effect.

## BUPRENORPHINE

Buprenorphine was first developed by Reckitt and Company, and the use of buprenorphine as an addiction therapy was demonstrated by Jasinski *et al.* in 1976 [93]. Krantz *et al.* first described substitution of buprenorphine in a patient who had demonstrated TdP and QTc prolongation on high dose (300mg/day) methadone and noted no significant increase in QTc with buprenorphine substitution

treatment [94]. There is a single case report in which a patient presented with prolonged QTc in the setting of drug overdose with several agents with QT prolonging potential [95]. A through QT study referenced in the package insert for transdermal buprenorphine demonstrated a maximal 9.2 msec (90% CI 5.2-13.3) increase in QT when applied at twice the maximum dose. [Package insert for Butrans (buprenorphine) transdermal system, revision 06/2011]. Aside from these citations, there are no studies suggesting QTc prolongation with buprenorphine, and most importantly there have been no reports of TdP associated with buprenorphine. Several studies prospective and cross-sectional in design have been published assessing the QT interval effects of buprenorphine. The first of these studies was by Fanoë *et al.* [51]. In this cross-sectional study, the authors not only demonstrated a significant association between methadone and QTc prolongation as well as an association syncope with higher doses of methadone but showed that in this cohort of 450 patients (43 patients on buprenorphine) no patients demonstrated a QTc >450 msec [51]. In the previously referenced study by Wedam *et al.*, buprenorphine treatment resulted in a nonsignificant increase in mean QTc over 16 weeks of  $5.4 \pm 4.1$  msec ( $p > 0.99$ ). No patients demonstrated categorical QTc prolongation (>470 in males and >490 in females) and no patients manifested a QTc >500 msec [30]. Anchersen *et al.* conducted a cross-sectional survey on Norwegian opioid maintenance treatment (OMT) patients between 2006 and 2007. Of the 200 patient's screened, 27 were treated with buprenorphine with mean dose of  $19 \pm 5$  mg and only 3 patients demonstrated a QTc >430 msec and no patients had a QTc >450 [56]. Also in 2008, Atanasos *et al.* published a case-control series assessing methadone and buprenorphine in OMT patients. The buprenorphine treated patients demonstrated a mean QTc of  $407 \pm 18$  msec (range 377-441 msec) that was not significant in comparison to healthy controls (mean QTc  $397 \pm 21$  sec, range 369-446 msec) [53]. Stallvik *et al.* more recently published a prospective assessment of buprenorphine and methadone in which 35 buprenorphine treated patients with a baseline mean QTc of  $405 \pm 19.5$  msec (350-450 msec) were treated with a mean dose of buprenorphine of  $18.7 \pm 3.8$  mg/day (range 16-20 mg/day) and demonstrated a mean QTc at six months of  $398 \pm 19.0$  msec (350-420 msec). As noted above, there are some questions regarding this latter study as the mean QTc in both the methadone and buprenorphine treated groups appears to have shortened which is difficult to explain [66]. Never the less, the data for buprenorphine indicates that although it has demonstrated weak  $I_{kr}/I_{HERG}$  inhibition, clinically it has no appreciable effect on cardiac repolarization. This is likely explained by buprenorphine's chemical structure which is similar to that of morphine, heroin and codeine (Fig. 2) and does not contain a freely mobile biphenyl structure.

## OXYCODONE

The first reported use of oxycodone was in 1917 in Germany for acute pain. The agent was derived from one of the phenanthrene opium alkaloids known as thebaine (Fig. 2) in 1916 [96]. Oxycodone shares a chemical structure similar to those of heroin, morphine, codeine and buprenorphine (Fig.

2). Fanoë *et al.*, as noted previously, has demonstrated that oxycodone is capable of weak  $I_{kr}/I_{HERG}$  inhibition and in a cohort of patients there was a dose dependent relationship between oxycodone dose and QTc, namely a 10 msec (95% CI 2-19) increase with a 100mg higher dose of oxycodone [17]. The specific mechanism whereby oxycodone inhibits  $I_{kr}/I_{HERG}$  is unclear. Aside from this particular study, there have only been three other case reports noting QTc prolongation particularly in the setting of oxycodone overdose. Berling *et al.* published a retrospective series of 137 patients treated for acute oxycodone overdose in which the majority of patients had taken sustained released preparations. Although no significant tachyarrhythmias were observed, the authors noted that 24 (18%) patients demonstrated bradycardia (HR < 60 BPM) with 5 patients (3.6%) had a heart rate < 50 BPM. Additionally, the authors noted that of the available EKGs (116) there were 20 patients (17%) with abnormal QT intervals [97]. Daniell presented a case report of a patient on relatively low doses of oxycodone who developed prolonged QTc and TdP in the setting of Taku-Tsubo cardiomyopathy. In this case, the direct association with oxycodone is difficult to make [98]. Baranchuk *et al.* presented a case of a patient treated with several agents to include morphine, escitalopram and oxycodone who manifested a QTc of 650 msec. It should be noted that the patient was bradycardic with wide complex ventricular escape rhythm that would significantly affect the measurement of the QT interval [99].

## CONCLUSION

*In vitro* data suggest that all opioids are capable of affecting cardiac electrophysiology in a deleterious manner, but the existing clinical data only support a reasonably strong case indicting LAAM and methadone. Nevertheless, the paucity of high quality data regarding the electrophysiological effects of opioids is concerning, particularly in the context of the increasing mortality associated with these agents. Only one randomized study comparing LAAM, methadone, and buprenorphine exists, and this study only acquired monthly electrocardiograms. Modern pharmacologic studies would require continuous, 24 hour monitoring to capture peak drug effects as well as to identify arrhythmias occurring during sleep, when the majority of deaths occur. The interaction of opioid-induced QT prolongation and hypoventilation has not been addressed in any context. Uncertainty exists regarding the best risk-mitigation strategy for QT prolonging agents as well. Only one study demonstrating the feasibility of electrocardiographic screening in an opioid addiction setting exists, and no data on the impact on mortality is available [100]. It is hoped that these issues will receive more attention in order to improve the safe use of opioids.

## DISCLAIMER

“The views expressed in this paper reflect the opinions of the authors only and not the official policy of the United States Navy, United States Army, Uniformed Services University, or the Department of Defense”.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENT

Declared none.

## REFERENCES

- [1] Brownstein M. A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci* 1993; 90: 5391-3.
- [2] Monahan BP, Ferguson CL, Killeavy ES, *et al.* Torsade de pointes occurring in association with terfenadine use. *JAMA* 1990; 264: 2788-90.
- [3] Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; 350: 1013-22.
- [4] United States Food and Drug Administration. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf>
- [5] <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>
- [6] Pert CB, Snyder S H. Opiate receptor: demonstration in nervous tissue. *Science* 1973; 179: 1011-4.
- [7] Simon EJ, Hiller JM, Edelman I. Stereospecific Binding of the Potent Narcotic Analgesic [31H] Etorphine to Rat-Brain Homogenate. *Proc Nat Acad Sci* 1973; 70(7): 1947-49.
- [8] Terenius L. Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. *Acta Pharmacol Toxicol (Copenh)* 1973; 32(3): 317-20.
- [9] Akil H, Madden J, Patrick RL, Barchas JD. in *Opiates and Endogenous Opioid Peptides*, ed. Kosterlitz, H. Elsevier, New York; 1976; 63-70.
- [10] Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* June 1976; 197: 517-32.
- [11] Lord JAH, Waterfield AA, Hughes J, Kosterlitz HW. Endogenous opioid peptides: multiple agonists and receptors. *Nature* 1977; 267: 495-9.
- [12] North RA, Williams JT, Surprenant A, Christie MJ.  $\mu$  and  $\delta$  receptors belong to a family of receptors that are coupled to potassium channels. *Proc Natl Acad Sci* 1987; 84: 5487-91.
- [13] Tsunoo A, Yoshii, M, Narahashi T. Block of calcium channels by enkephalin and somatostatin in neuroblastoma-glioma hybrid NG108-15 cells. *Proc Natl Acad Sci U S A* 1986; 83: 9832-6.
- [14] Deamer RL, Wilson DR, Clark DS, Prichard JG. Torsade de pointes associated with high dose levomethadyl acetate (ORLAAM). *J Addict Dis* 2001; 20: 7-14.
- [15] Katchman AN, McGroary KA, Kilborn MJ, *et al.* Influence of opioid agonists on cardiac Human *ether-a-go-go* related gene  $K^+$  currents. *JPET* 2002; 303: 688-94.
- [16] Zünkler BJ, Wos-Maganga M. Comparison of the effects of methadone and heroin on human ether-à-go-go-related gene channels. *Cardiovasc Toxicol* 2010; 10(3): 161-5.
- [17] Fanoë S, Jensen GB, Sjogren P, Korsgaard MPG, Grunnet M. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity *in vitro*. *Br J Clin Pharmacol* 2009; 67(2): 172-9.
- [18] Kang J, Chen XL, Wang H, Rampe D. Interactions of the narcotic l- $\alpha$ -acetylmethadol with human cardiac  $K^+$  channels. *Eur J Pharmacol* 2003; 458(1-2): 25-9.
- [19] Jaffe JH, Senay EC, Schuster CR, Renault PR, Smith B, DiMenza S. Methadyl acetate vs. methadone: A doubleblind study in heroin users. *JAMA* 1972; 222: 437-42.
- [20] Senay EC, Dorus W, Renault RF. Methadylacetate and methadone: An open comparison. *JAMA* 1977; 237: 138-42.
- [21] Trueblood B, Judson BA, Goldstein A. Acceptability of methadyl acetate (LAAM) as compared with methadone in a treatment program for heroin addicts. *Drug Alcohol Depend* 1978; 3: 125-32.
- [22] Freedman RR, Czertko G. A comparison of thrice weekly LAAM and daily methadone in employed heroin addicts. *Drug Alcohol Depend* 1981; 8: 215-22.
- [23] Glanz M, Klawansky S, McAulliffe W, Chalmers T. Methadone vs. L-alpha-acetyl-methadol (LAAM) in the treatment of opiate addiction. A meta-analysis of the randomized, controlled trials. *Am J Addict* 1997; 6(4): 339-49.
- [24] Clark N, Lintzeris N, Gijsbers A, Whelan G, Dunlop A, Ritter A, Ling W. LAAM maintenance vs methadone maintenance for heroin dependence. *Cochrane Database Syst Rev* 2002; (2): CD002210.
- [25] Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 2000; 343(18): 1290-7.
- [26] Eissenberg T, Bigelow GE, Strain EC, *et al.* Dose-related efficacy of levomethadyl acetate for treatment of opioid dependence: a randomized clinical trial. *JAMA* 1997; 277(24): 1945-51.
- [27] Oliveto AH, Farren C, Kosten TR. Effect of LAAM dose on opiate use in opioid dependent patients: a pilot study. *Am J Addict* 1998; 7(4): 272-82.
- [28] United States Food and Drug Administration. Letter to addiction treatment specialists. April 11, 2001; <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173871.pdf>
- [29] European Agency for the Evaluation of Medical Products. EMEA public statement to suspend the marketing authorisation for Orlaam(levoacetylmethadol) in the European Union. April 19, 2001; [www.ema.europa.eu/docs/en\\_GB/document\\_library/Public\\_statement/2009/12/WC500018335.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018335.pdf)
- [30] Wedam E, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MCP. QT-Interval Effects of Methadone, Levomethadyl, and Buprenorphine in a Randomized Trial. *Arch Intern Med* 2007; 167(22): 2469-75.
- [31] Wieneke H, Conrad H, Wolstein J, *et al.* Levo-alpha-acetylmethadol (LAAM) induced QTc-prolongation - results from a controlled clinical trial. *Eur J Med Res* 2009; 14(1): 7-12.
- [32] Gerlach R. A brief overview on the discovery of methadone. IN-DRO e.V. Muenster 2004. Web-publication at [www.indro-online.de/discovery.pdf](http://www.indro-online.de/discovery.pdf)
- [33] Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. *JAMA* 1965; 193: 80-4.
- [34] Dole VP, Nyswander M. Heroin addiction: A metabolic disease. *Arch Intern Med* 1967; 120: 19-24.
- [35] Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf* 2005; 14(11): 747-53.
- [36] Poluzzi E, Raschi E, Moretti U, De Ponti F. Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System(AERS). *Pharmacoepidemiol Drug Saf* 2009; 18(6): 512-8.
- [37] Krantz MJ, Lewkowicz L. Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsades de Pointes associated with very high doses methadone. *Ann Intern Med* 2002; 137: 501-4.
- [38] Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 2003; 23(6): 802-5.
- [39] Justo D, Gal-Oz A, Paran Y, Goldin Y, Zeltser D. Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction* 2006; 101(9): 1333-8.
- [40] Martell BA, Arnsten JH, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; 139(2): 154-5.
- [41] Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol* 2005; 95(7): 915-8.
- [42] Reddy S, Hui D, El Osta B, *et al.* The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study. *J Palliat Med* 2010; 13(1): 33-8.
- [43] Heppel DB, Haigney MCP, Krantz MJ. The effect on Oral Methadone on the QTc Interval in Advanced Cancer Patients: A Prospective Pilot Study; Letters to the Editor. *J Palliat Med* 2010; 13(6): 38-9.
- [44] Gil M, Sala M, Anguera I, *et al.* QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol* 2003; 92(8): 995-7.
- [45] Kornick CA, Kilborn MJ, Santiago-Palma J, *et al.* QT interval prolongation associated with intravenous methadone. *Pain* 2003; 105: 499-506.
- [46] Piguet V, Desmeules J, Ehret G, Stoller R, Dayer P. QT interval prolongation in patients on methadone with concomitant drugs. *J Clin Psychopharmacol* 2004; 24(4): 446-8.



- [47] Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. QTc interval prolongation in patients on long-term methadone maintenance therapy. *Eur Addict Res* 2005; 11(1): 44-9.
- [48] Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH. Effects of methadone on QT-interval dispersion. *Pharmacotherapy* 2005; 25(11): 1523-9.
- [49] Ehret GB, Voide C, Gex-Fabry M, *et al.* Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Arch Intern Med* 2006; 166(12): 1280-7.
- [50] Fanoë 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): 1051-5.
- [51] Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study. *Addiction* 2007; 102(2): 289-300.
- [52] Athanasos P, Farquharson AL, Compton P, Psaltis P, Hay J. Electrocardiogram characteristics of methadone and buprenorphine maintained subjects. *J Addict Dis* 2008; 27(3): 31-5.
- [53] Patel AM, Singh JP, Ruskin JN. Role of implantable cardioverter-defibrillators in patients with methadone-induced long QT syndrome. *Am J Cardiol* 2008; 101(2): 209-11.
- [54] Fonseca F, Marti-Almor J, Pastor A, *et al.* Prevalence of long QTc interval in methadone maintenance patients. *Drug Alcohol Depend* 2009; 99(1-3): 327-32.
- [55] 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): 993-9.
- [56] Fareed A, Vayalappalli S, Byrd-Sellers J, *et al.* Onsite QTc interval screening for patients in methadone maintenance treatment. *J Addict Dis* 2010; 29(1): 15-22.
- [57] Huh B, Park CH. Retrospective analysis of low-dose methadone and QTc prolongation in chronic pain patients. *Korean J Anesthesiol* 2010; 58(4): 338-43.
- [58] Hanon S, Seewald RM, Yang F, Schweitzer P, Rosman J. Ventricular arrhythmias in patients treated with methadone for opioid dependence. *J Interv Card Electrophysiol* 2010; 28(1): 19-22.
- [59] Anchersen K, Hansteen V, Gossop M, Clausen T, Waal H. Opioid maintenance patients with QTc prolongation: congenital long QT syndrome mutation may be a contributing risk factor. *Drug Alcohol Depend* 2010; 112(3): 216-9.
- [60] Mayet S, Gossop M, Lintzeris N, Markides V, Strang J. Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation? *Drug Alcohol Rev* 2011; 30(4): 388-96.
- [61] Perrin-Terrin A, Pathak A, Lapeyre-Mestre M. QT interval prolongation: prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. *Fundam Clin Pharmacol* 2011; 25(4): 503-10.
- [62] Roy AK, McCarthy C, Kiernan G, *et al.* Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction* 2012; 107(6): 1132-9.
- [63] Chang KC, Huang CL, Liang HY, *et al.* Gender-specific differences in susceptibility to low-dose methadone-associated QTc prolongation in patients with heroin dependence. *J Cardiovasc Electrophysiol* 2012; 23(5): 527-33.
- [64] Demarie D, Marletta G, Imazio M, *et al.* Cardiovascular-associated disease in an addicted population: an observation study. *J Cardiovasc Med (Hagerstown)* 2011; 12(1): 51-4.
- [65] Stallvik M, Nordstrand B, Kristensen O, Bathen J, Skogvoll E, Spigset O. Corrected QT interval during treatment with methadone and buprenorphine-Relation to doses and serum concentrations. *Drug Alcohol Depend* 2013; 129(1-2): 88-93.
- [66] Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. *NCHS Data brief* 2009; (22): 1-8.
- [67] Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006; 31(6): 506-11.
- [68] 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. *Am J Med* 2008; 121(1): 66-71.
- [69] Vormfelde SV, Poser W. Death attributed to methadone. *Pharmacopsychiatry* 2001; 34(6): 217-22.
- [70] Heinemann A, Iwersen-Bergmann S, Stein S, Schmoldt A, Püschel K. Methadone-related fatalities in Hamburg 1990-1999: implications for quality standards in maintenance treatment? *Forensic Sci Int* 2000; 113(1-3): 449-55.
- [71] Caplehorn JR. Deaths in the first two weeks of maintenance treatment in NSW in 1994: Identifying cases of iatrogenic methadone toxicity. *Drug Alcohol Rev* 1998; 17: 9-17.
- [72] Dyer KR, White JM. Patterns of symptom complaints in methadone maintenance patients. *Addiction* 1997; 92(11): 1445-55.
- [73] Dyer KR, Foster DJ, White JM, Somogyi AA, Menelaou A, Bochner F. Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: comparison of those who do and do not experience withdrawal and concentration-effect relationships. *Clin Pharmacol Ther* 1999; 65(6): 685-94.
- [74] Dyer KR, White JM, Foster DJ, Bochner F, Menelaou A, Somogyi AA. The relationship between mood state and plasma methadone concentration in maintenance patients. *J Clin Psychopharmacol* 2001; 21(1): 78-84.
- [75] Eap CB, Finkbeiner T, Gastpar M, Scherbaum N, Powell K, Baumann P. Replacement of (R)-methadone by a double dose of (R,S)-methadone in addicts: interindividual variability of the (R)/(S) ratios and evidence of adaptive changes in methadone pharmacokinetics. *Eur J Clin Pharmacol* 1996; 50(5): 385-9.
- [76] Foster DJ, Somogyi AA, Dyer KR, White JM, Bochner F. Steady-state pharmacokinetics of (R)- and (S)-methadone in methadone maintenance patients. *Br J Clin Pharmacol* 2000; 50(5): 427-40.
- [77] Eap CB, Bertschy G, Baumann P, Finkbeiner T, Gastpar M, Scherbaum N. High interindividual variability of methadone enantiomer blood levels to dose ratios. *Arch Gen Psychiatry* 1998; 55(1): 89-90.
- [78] Eap CB, Bourquin M, Martin J, *et al.* Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Depend* 2000; 61(1): 47-54.
- [79] Eap CB, Crettol S, Rougier JS, *et al.* Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther* 2007; 81(5): 719-28.
- [80] Lin C, Somber T, Molnar J, Somber J. The effects of chiral isolates of methadone on the cardiac potassium channel IKr. *Cardiology* 2009; 113(1): 59-65.
- [81] Skjervold B, Bathen J, Spigset O. Methadone and the QT interval: relations to the serum concentrations of methadone and its enantiomers (R)-methadone and (S)-methadone. *J Clin Psychopharmacol* 2006; 26(6): 687-9.
- [82] Ansermot N, Albayrak O, Schlöpfer J, *et al.* Substitution of (R,S)-methadone by (R)-methadone: Impact on QTc interval. *Arch Intern Med* 2010; 170(6): 529-36.
- [83] Kapur BM, Hutson JR, Chibber T, Luk A, Selby P. Methadone: a review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci* 2011; 48(4): 171-95.
- [84] Hassan HE, Myers AL, Coop A, Eddington ND. Differential Involvement of P-Glycoprotein (ABCB1) in the permeability, Tissue Distribution, and Antinociceptive Activity of Methadone, Buprenorphine, and Diprenorphine: *In Vitro* and *In Vivo* Evaluation. *J Pharm Sci* 2009; 98(12): 4928-40.
- [85] Zuklyazminskaya EV, Abriel H. Prevalence of significant genetic variants in congenital long QT syndrome is largely underestimated. *Front Pharmacol* 2012; 3(72): 1-3.
- [86] Kuryshv YA, Bruening-Wright A, Brown AM, Kirsch GE. Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. *J Cardiovasc Pharmacol* 2010; 56(4): 420-30.
- [87] Lintzeris N, Mitchell TB, Bond A, Nestor L, Strang J. Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. *J Clin Psychopharmacol* 2006; 26(3): 274-83.
- [88] Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug Alcohol Depend* 2007; 91(2-3): 187-94.
- [89] Wang D, Teichtahl H, Drummer O, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; 128(3): 1348-56.
- [90] Gillis AM, Stoohs R, Guilleminault C. Changes in the QT interval during obstructive sleep apnea. *Sleep* 1991; 14(4): 346-50.

- [91] Monahan K, Storfer-Isser A, Mehra R, *et al.* Triggering of nocturnal arrhythmias by sleep-disordered breathing events. *J Am Coll Cardiol* 2009; 54(19): 1797-804.
- [92] Schwartz PJ, Priori SG, Spazzolini C, *et al.* Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; 103(1): 89-95.
- [93] Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann NY Acad Sci* 2012; 1248: 124-39.
- [94] Krantz MJ, Garcia JA, Mehler PS. Effects of buprenorphine on cardiac repolarization in a patient with methadone-related Torsades de Pointes. *Pharmacother* 2005; 25(4): 611-14.
- [95] Baker JR, Best AM, Pade PA, McCance-Katz EF. Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. *Ann Pharmacother* 2006; 40(3): 392-6.
- [96] Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; 29(5 Suppl): S47-56.
- [97] Berling I, Whyte IM, Isbister GK. Oxycodone overdose causes nalaxone responsive coma and QT prolongation. *QJM* 2013; 106(1): 35-41.
- [98] Daniell HW. Torsades-de-Pointes associated with Taku-Tsubo cardiomyopathy following greatly reduced oxycodone use in an elderly woman. *J Opioid Manage* 2011; 7(2): 155-9.
- [99] Baranchuk A, Simpson CS, Methot M, Gibson K, Strum D. Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines. *Can J Cardiol* 2008; 24(7): e38-40.
- [100] Katz DF, Sun J, Khatri V, *et al.* QTc interval screening in an opioid treatment program. *Am J Cardiol* 2013; 112(7): 1013-8.