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Comprehensive review on methadone-induced QT prolongation and torsades

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Abstract

An alternative analgesic to morphine is methadone, which is used to control chronic pain and is used in opioid rehabilitation treatment programs due to methadone having a long half-life and being relatively inexpensive as compared to extended-release forms of morphine. Despite its benefits, methadone accumulates in adipose tissue due to being lipophilic, binds strongly to plasma proteins, and is metabolized in the liver by the cytochrome P450 system causing methadone levels to be variable and subject to influence according to the individual body compositions and concurrent use of cytochrome P450 inhibitors. In addition to methadone being able to cause both respiratory and central nervous system depression, methadone can also prolong the QT interval and cause potentially life-threatening arrhythmias including torsades de pointes. The susceptibility of unintentional overdosing of methadone due to its varied pharmacologic properties and potentially fatal induction of arrhythmias may cause the risks of methadone use to

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outweigh its benefits and therefore must be closely monitored.

Keywords: Analgesic, dysrhythmia, methadone, opioid, torsade de pointes

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Introduction

Methadone was originally formulated in 1938 in Germany.[1] Methadone is increasingly used in palliative medicine and in opioid abuse rehabilitation programs to control chronic intractable pain and to assist patients through detoxification while mitigating the effects of withdrawal from opioid abuse. Methadone is an inexpensive and long-acting, potent analgesic that is effective in the treatment of chronic pain and substance abuse.[2]

Mounting evidence exists about the arrhythmogenic potential of methadone via the prolongation of the QT interval and subsequent increase in risk of inducing the potentially fatal arrhythmia, torsades de pointes (TdP).[3],[4] In this article, the impact of methadone-inducing potentially fatal arrhythmias in the settings of chronic pain management and in opioid abuse rehabilitation is discussed.

Discussion

Methadone use to control chronic pain

Due to its long half-life, methadone is commonly used for the treatment of opioid addiction as well as for the treatment of

chronic pain, especially in terminally ill cancer patients.[5] Methadone may be used to control pain in patients who have comorbid delirium and renal failure because methadone lacks active metabolites, which differentiates methadone from morphine, as the active metabolites of morphine accumulate in patients with renal failure and cause worsening delirium and altered mental status. In addition to lacking active metabolites, there are no dose adjustments of methadone needed for patients with renal impairment as opposed to morphine.[6] The main contraindications of methadone are respiratory depression, central nervous system (CNS) depression, and allergy to either the drug or the preservatives used in its preparation. Caution is essential when treating patients with methadone who are suffering from increased intracranial pressure, severe asthma, or chronic obstructive pulmonary disease since methadone can exacerbate these conditions.[4] Methadone is significantly less expensive than controlled extended-release forms of morphine. Constipation, nausea, and vomiting are also less common side effects of methadone as opposed to morphine.[7] A comparison between methadone and morphine is outlined in [Table 1].[4],[5],[6],[7],[8],[9],[10],[11],[12]

	Methadone	Morphine
Receptors affected in the brain	Agonistic effect: Mu (μ) and delta (δ) receptors Competitive antagonist effect: NMDA receptors	Pure mu (μ) receptor agonists
Potency	More potent	Less potent
Tolerance susceptibility	Less risk	More risk
Active metabolites	No	Yes
Renal adjustment needed	No	Yes
Contraindications	Respiratory depression, CNS depression, allergy	Respiratory depression, CNS depression, allergy
Cost	Inexpensive	Expensive
Side effects: Constipation, nausea, vomiting	Less common	More common

Methadone does not have active metabolites and does not require renal dosing. Methadone and morphine have similar contraindications, but the cost of methadone is less than morphine and the side effects, although similar, are less common for methadone. CNS=Central nervous system, NMDA=N-methyl-D-aspartate

Table 1: Methadone compared to morphine[4],[5],[6],[7],[8],[9],[10],[11],[12]

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Pharmacokinetics of methadone

Methadone is a lipophilic medication with a large volume of distribution and high tissue-binding affinity. Due to these factors and its long half-life, methadone tends to accumulate in adipose tissues, especially after repeated doses, and causes methadone toxicity to be more prone to develop, even with appropriately monitored use.[5] In the bloodstream, methadone is 60%–90% bound to plasma proteins, and its bioavailability after oral administration is around 70%–90%. The maximum plasma concentration is reached after 3–4 h following oral administration. On average, the half-life of methadone is around 24 h, but it may vary as much as from 8 to 120 h depending on an individual patient's adipose tissue composition. However, its analgesic effect only lasts between 6 and 12 h,[13] which means that to achieve an appropriate analgesic effect, one would likely need to dose more frequently. This frequent dosing could potentially lead to accumulation of methadone in the body and predispose to the development of toxicity.[1]

Methadone is metabolized mainly in the liver by the cytochrome P450 system,[14] which causes methadone to be susceptible to interaction with other medications, especially those that inhibit the cytochrome P450 system, such as ciprofloxacin, fluconazole, and fluoxetine. The concurrent use of methadone with cytochrome P450 inhibitors can cause an elevation of methadone serum levels and therefore increase the risk of methadone toxicity with potentially life-threatening side effects, such as respiratory depression and cardiac arrhythmias. Being heavily bound to plasma

proteins is a source of possible drug interactions with methadone. In the setting of low levels of plasma protein, the concurrent use of medications that affect plasma protein levels or concurrent use of medications that compete for plasma protein binding may cause an increase in the propensity for adverse reactions secondary to methadone to develop by increasing the unbound active level of methadone in the bloodstream.[5]

Dosing of methadone

Understanding the pharmacokinetics and chemistry of methadone in relation to other opioids is essential to the successful use of methadone in the clinical setting. Methadone is a lipophilic drug with a large volume of distribution that has a biphasic course of elimination, which includes a fast phase of tissue distribution that is followed by a slower metabolism phase.[15],[16] Following repetitive doses of methadone, tissue storage levels of methadone increase, thus acting as a secondary source of continuous drug release of methadone into the bloodstream between scheduled oral doses of the medication.[17],[18] Metabolic tolerance to methadone through hepatic auto-induction may also develop.[19] To achieve an adequate analgesic effect while avoiding drug toxicity, the frequency and dose of methadone administration need to be adjusted according to the patient's clinical status by balancing the analgesic effect of methadone against the medication's adverse reactions, including respiratory and CNS depression, which suggest the onset of methadone toxicity. Methadone dose and frequency adjustments should not be based on methadone plasma levels, which have proven to be of limited utility.[18]

Methadone has an agonistic effect on mu (μ) and delta (δ) receptors in the brain. Methadone also has a competitive antagonist effect on N-methyl-D-aspartate (NMDA) receptors, which are responsible for opioid tolerance and neuropathic pain. Given this, methadone is more potent and carries a lower chance of tolerance compared to pure μ receptors agonists such as morphine, thus making dose conversion between methadone and other opioids challenging.[7],[8],[9],[10],[20]

Methadone use in palliative care and in opioid abuse rehabilitation

Methadone use for the treatment of chronic pain is well established in the palliative care population due to its low cost, long half-life, and its added effectiveness of addressing neuropathic pain through competitive antagonistic activity on NMDA receptors.[1]

While methadone shares the same side effect profile as other opioids, methadone causes less constipation and less tolerance when compared to other opioids, which makes it a suitable drug for use in palliative care medicine.[11] In addition to the side effects of constipation as well as respiratory and CNS depression such as other opioid medications, methadone also is arrhythmogenic through the prolongation of the QT interval on the patient's electrocardiogram (ECG).[2]

Prolonged QT syndrome

The QT interval on the ECG is measured between the first deflection of the QRS complex and the end of the T-wave. It represents the interval during which the myocardial membrane channels are activated during depolarization followed by repolarization of the ventricles. Although there is no consensus about the exact cutoff value for the normal QT segment, most authors agree that the accepted normal values for the QT interval are <430 ms in men and <450 ms in women.[21] The QT interval varies with the heart rate; thus, it is corrected according to heart rate and is referred to as corrected QT interval (QTc). Although different formulae are used to calculate the QTc interval, the most widely used formula is Bazett's formula, which is calculated by dividing the QT interval in milliseconds by the square root of the interval between two consecutive R-waves (RR interval) in milliseconds and is represented by the following formula: QTc = QT in milliseconds $\sqrt{RR}$.[22] A prolonged QT interval predisposes an individual to a potentially fatal arrhythmia called TdP.[2]

Causes of a prolonged QT interval may be congenital or acquired. The primary cause of congenital long QT syndrome (LQTS) involves a human ether-a-go-go-related gene (hERG) and a subunit of the voltage-gated potassium channels found predominantly in the myocardial tissue, which is where the hERG gene is most active. These voltage-gated potassium channels are the predominant facilitator of the delayed-rectifier potassium currents (IK) and are active in Phase 3 of the action potential (AP), which causes repolarization of the ventricles. An abnormality in these voltage-gated potassium channels leads to a prolonged AP and subsequent prolongation of the QT interval, as seen in [Figure 1].[2] Congenital LQTS has an incidence of approximately 1:2500 in the general population and may be undiagnosed until the patient is exposed to a medication known to prolong the QT interval, particularly in pediatric patients.[23] Approximately 10%–15% of patients with medication-induced LQTS have concurrent underlying congenital LQTS, which exacerbates the risk for these patients to manifest LQTS when exposed to medications that increase the QT interval.[24] It is also estimated that around 12% of infants who die from sudden infant death syndrome have congenital QT interval prolongation as the underlying pathology.[25]

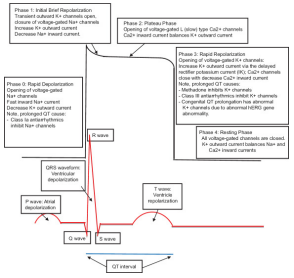

Figure 1: Phases of an action potential in a ventricular myocyte with corresponding surface electrocardiogram, electrolyte currents, and active ion channels[2],[37],[38],[39],[40]

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Acquired LQTS usually results from the use of particular medications or from electrolyte imbalances such as hypokalemia, hypomagnesaemia, or hypocalcemia. Bradycardia can also increase the risk of drug-induced LQTS.[26] The list of medications that can cause prolongation of the QT interval is extensive, and the most common QT-prolonging medications are summarized in [Table 2]. The most well-known medications that cause QT prolongation include macrolide and fluoroquinolone antibiotics. Other medications known to frequently cause prolonged QT intervals include antihistamines, antidepressants, and antipsychotics.[27] Methadone in high doses or when administered intravenously may cause QT prolongation.[27]

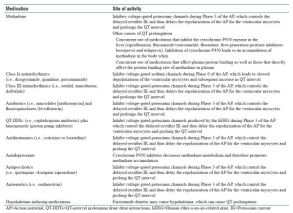

Table 2: Medications that prolong the QT interval[32],[33],[37],[38],[39],[42],[43],[44],[45],[46],[47],[48],[49],[50]

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A prolonged QT interval is a proarrhythmic state that is associated with an increased risk of ventricular arrhythmia, particularly TdP. TdP is a form of ventricular tachycardia of varying polarity that can either resolve spontaneously or degenerate into ventricular fibrillation, which is a potentially fatal arrhythmia and is the most feared outcome from the development of a prolonged QT interval.[28],[29]

Methadone and prolonged QT syndrome

Although methadone has been used for several decades as a preferred agent for the treatment of opioid dependence and as a strong analgesic agent in the treatment of chronic pain in palliative medicine settings, attention toward the cardiac effects of methadone is a relatively recent phenomenon. The first report of methadone-associated TdP was published in 2002 by Krantz *et al*.[4] However, by this time, TdP was an already known side effect of other opioid analgesic agents, including levomethadyl hydrochloride acetate, which is a derivative of methadone, and was previously used as a long-term opioid analgesic, but was withdrawn from Europe in 2001 and from the United States in 2003 because of its effect on prolongation of the QT interval.[30],[31],[32] Following the initial report of TdP secondary to QT interval prolongation by methadone in 2002, methadone has been assessed thoroughly through cross-sectional, retrospective, and prospective studies designed specifically to evaluate the clinical association of methadone and TdP induction via QT prolongation, which has become even more important due to the dramatic increase in the use of methadone in clinical practice since 1997.[33]

Among opioid-dependent patients with structurally normal hearts, the highest rate of sudden deaths is in patients who regularly use methadone.[34] This finding elevated the level of suspicion regarding the possibility of a nonstructural etiology, such as an induced electrical arrhythmia caused by methadone, as the etiology of sudden death in these patients. A study that was performed in West Virginia found that in 2006, methadone was associated with 40% of the opioid-related deaths despite methadone being prescribed less frequently than other opioids.[35] It has also been reported that from 1997 to 2005, methadone-related deaths increased by 468%,[36] which also correlates with the dramatic increase in methadone use since 1997. However, the increase in methadone-related deaths since 1997 is not exclusively due to the arrhythmogenic nature of methadone but is also due to methadone abuse, overdose, and in some instances, from respiratory depression related to the lack of experience and knowledge of methadone's pharmacokinetics by prescribers.[36]

Mechanism of prolonged QT and torsades de pointes

Understanding the cardiac ECG and the corresponding phases of the AP of ventricular myocytes facilitates appreciation of the mechanism of drug-induced QT prolongation and the development of TdP. The QT interval on the ECG corresponds to the time between ventricular depolarization, denoted by the QRS-wave complex on the ECG, followed by ventricular repolarization, denoted by the T-wave on the ECG, from Phase 0 through Phase 3 on the corresponding AP, as seen in [Figure 1].[37],[38],[39],[40]

Although medication-induced QT prolongation may affect different phases of the AP to cause QT prolongation, medications that induce QT prolongation affect Phase 3 most commonly,[41] as outlined in [Table 2]. Class Ia antiarrhythmic medications, including disopyramide, quinidine, and procainamide, inhibit voltage-gated sodium channels and therefore slow the Phase 0 depolarization of the AP, thereby causing an increase in AP duration and subsequently prolonging the QT interval. Class III antiarrhythmic medications, such as sotalol, amiodarone, and dofetilide, inhibit the voltage-gated potassium channels in Phase 3 of the AP, causing prolongation of the repolarization of the AP of the ventricle with an increase QT prolongation.[42],[43],[44],[45],[46],[47],[48],[49],[50]

Due to the concern for medication-induced QT prolongation, the United States Food and Drug Administration (FDA) have issued warnings about this potential adverse reaction for several of the medications listed in [Table 2]. For example, in 2013, the FDA issued a warning about the potential of the antibiotic azithromycin to cause QT prolongation and therefore increase the risk of TdP.[51] Guidelines have been developed by the FDA for the assessment of medication-induced LQTS in the evaluation of new medications, and any medication that increases the QT/QTc interval by ≥20 ms is unlikely to be approved.[52] A study performed in 2016 assessed the incidence of QT prolongation and the concurrent use of the following medications that are known to prolong the QT interval, ceftriaxone and lansoprazole. The study found that when these two QT-prolonging medications were used together, the incidence of QT prolongation was higher than the incidence of QT prolongation of patients using either medication separately.[41] In practice, providers are advised to avoid combining the use of multiple QT-prolonging medications.[37]

Multiple animal models have been studied to identify the mechanism by which methadone causes QT prolongation. Similar to congenital QT interval prolongation, methadone-induced QT prolongation is caused by the inhibition of the hERG product, the voltage-gated potassium channels, which control the delayed-rectifier IK present in Phase 3 of the AP. Inhibiting the voltage-gated potassium channels by methadone increases the time to repolarization and leads the AP, and therefore the corresponding QT interval, to both be prolonged.[55],[56] Other possible mechanisms of methadone-induced QT prolongation include repetitive depolarization,[57] bradycardia secondary to blockage of calcium channel,[43],[58] and anticholinergic effects. The presence of a premature beat after a long RR interval would be able to induce an arrhythmia, thus explaining why bradycardia is a risk factor for TdP induction. Methadone also is associated with an increase in risk of sleep apnea,[44] which is another possible proarrhythmic factor of methadone, as sleep apnea is known to be associated with both bradycardia and QT prolongation.[45],[46]

Incidence of QT prolongation and torsades de pointes with methadone use

The true incidence rate of QT prolongation and TdP with methadone use is difficult to determine. First, the existence of different reference values used by various authors to define QT prolongation affect the reported incidence rate as there is not a consistent cutoff value for a normal QT interval. Despite the use of different reference values, the overall risk of TdP is directly associated with the extent of the QT prolongation with more than 90% of events occurring when the QT interval exceeds 500 ms and rarely occurs when the QT interval is <500 ms.[1],[53],[59] Second, individuals have variable complicating risk factors that predispose them to the development of QT prolongation and subsequent TdP. Some individuals have undiagnosed congenital prolonged QT syndrome. Other individuals display variable liver metabolism of methadone. Individuals with 6*/6* genotype of CYP2B6 hepatic enzyme who take methadone are more likely to develop prolonged QT intervals than the rest of the population.[60] This is due to these patients having difficulty metabolizing the S-methadone enantiomer, the most potent portion of methadone that effectively blocks the potassium channels in Phase 3 of the AP, by their liver.[61]

Additional risk factors for prolongation of the QT interval often exist in patients who are found to have both QT prolongation, and exposure to methadone, which causes difficulty in determining the extent that methadone alone, contributes to QT prolongation. In a review by Justo *et al*. of patients experiencing prolonged QT with methadone treatment, 100% had at least one additional risk factor and 85% had at least two other risk factors for QT prolongation.[62]

The incidence of QT prolongation in the setting of methadone exposure is not rare as seen in [Table 3].[63],[64],[65],[66],[67],[68] Despite the fact that QT prolongation is not a rare phenomenon, the development of TdP is rare with a reported incidence of 0.06/100 patient-years [65] or up to 3.6% of patients with methadone exposure.[54],[67] Among those patients who develop TdP, high dosages of methadone is the most prevalent risk factor, and the second most prevalent risk factor in men is concurrent use of other medications that are also known to induce QT prolongation and in women is hypokalemia.[69]

Length of QT interval (ms)	Incidence (%)
>430	41-49
>450	19-29
>470	7-15
>500	1.8-16.2

QT prolongation with methadone exposure is not rare

Table 3: Incidence of QT prolongation with methadone exposure[64],[65],[66],[67],[68],[69]

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Another point of debate is whether the dose of methadone or whether serum methadone levels correlate to the extent of QT prolongation. While some researchers have found that a methadone dose-to-QT prolongation relationship exists,[70],[71],[72],[73],[74] other studies have failed to show the same relationship.[66],[75]

Interestingly, progressive prolongation of QT over time, even with a stable dose of methadone, has also been reported.[76],[77] This is not necessarily surprising given the adipose tissue accumulation of methadone and subsequent continual release of methadone into the bloodstream that may occur between oral methadone doses. Kornick *et al*. studied the effects of intravenous methadone and found that there was no minimally safe dose of intravenous methadone and that QT

prolongation may occur with dosages as small as 0.4 mg/h, but this study suggested that QT prolongation may have been due to the preservatives used in the intravenous methadone preparation and not exclusively due to methadone itself.[78]

The QT interval prolongation >500 ms occurs most often in patients who have multiple risk factors for QT prolongation and in patients that receive high dosages of methadone. Despite the extent of QT prolongation, the incidence of TdP remains rare.[65]

Predisposing risk factors for the development of QT prolongation and torsades de pointes with methadone use

The following risk factors increase a patient's susceptibility to developing prolonged QT and TdP when using methadone: female gender,[69],[79] increasing age >65 years old,[79] congenital LQTS, liver and renal disease, hemodialysis,[80] anorexia nervosa, starvation, malnutrition,[75] sleep apnea,[70] and cardiac disease (including heart failure, ischemic heart disease, left ventricular hypertrophy, and dilatation).[60],[62],[66],[69],[70],[81],[82] Approximately 70% of patients with LQTS are female, which is thought to be due to testosterone having a QT shortening effect, thus causing females with low testosterone to be at an elevated risk for prolonged QT intervals.[29] Electrolyte imbalances is an important risk factor for the prolongation of QT intervals, including hypokalemia (potassium <3.5 mEq/L),[69] hypocalcemia (calcium level <8.5 mg/dL),[74] and hypomagnesaemia (magnesium level <1.8 mEq/L).[83]

Human immunodeficiency virus (HIV) patients were also found to be particularly predisposed to prolonged QT intervals, due in part to the HIV infection itself,[63] as well as due to the concurrent presence of liver disease, hepatitis C infection, high rates of drug abuse in HIV patients, such as cocaine and heroin,[64],[65],[66],[67] malnutrition, electrolyte imbalances, [74],[82],[80] and concurrent use of antiviral medications for the treatment of HIV (especially protease inhibitors).[39],[68] In one study, even fluctuation of blood glucose between hyperglycemia and hypoglycemia was demonstrated to predispose a patient to QT prolongation.[47]

Screening recommendation

Providers need to be keenly aware of the potential for the development of QT prolongation and possible TdP in patients who take methadone to ensure that appropriate monitoring of patients while, on methadone, is achieved to mitigate adverse events. One study found only 41% of physicians knew about the QT prolongation risks of methadone, and only 24% were aware of the risk of TdP with methadone use.[84] All providers, whether they prescribe methadone or care of patients who take methadone prescribed by another provider, need to be aware of its potential to induce QT prolongation as the extent of QT prolongation has been seen to be exacerbated not only with elevated doses of methadone but also with concurrent use of medications that affect methadone metabolism, protein binding of methadone, electrolyte imbalances, and concurrent use of methadone and other QT-prolonging medications. Providers need to be aware of the potential of methadone to prolong the QT interval and need to be cautious when prescribing additional medications for these patients. A 2017 study looked at the level of QT prolongation risk assessment via ECG was performed on patients admitted to an inpatient psychiatric hospital unit. These patients potentially were prescribed antipsychotic medications

known to prolong the QT interval and may also have had concurrent exposure to other QT-prolonging medications including methadone. The rate of QT interval evaluation via ECG in this study was ≤20%.[85] This low rate of QT interval evaluation in the setting of QT-prolonging medication exposure is particularly concerning given that the rate of sudden cardiac death is elevated in mental health patients.[85]

Before prescribing methadone for a patient, providers should screen patients for risk factors for the development of QT interval prolongation so that QT-prolonging medications, including methadone, can be avoided if possible. A comprehensive patient history and physical examination is the first step to identify patients at risk for developing QT prolongation. Concerning symptoms that may be suggestive of cardiac etiology, such as dizziness, palpitation, or syncope, need to be identified. Previous illnesses, such as cardiac, liver, and kidney diseases, also need to be discussed with patients as these conditions increase the risk of developing QT prolongation as well. Personal habits that may contribute to negative outcomes in methadone treatment, such as smoking, drug abuse, and alcohol consumption, need to also be addressed. An extensive review of the patient's current medications is paramount to identify any that may potentially interact with methadone or that may also cause QT prolongation. The family history is of extreme importance when evaluating a patient for initiating methadone therapy due to the possibility of certain patients being genetically susceptible to methadone's adverse effects. Younger patients may have undiagnosed congenital LQTS but may be asymptomatic with a normal baseline ECG at presentation before exposure to QT-prolonging medications such as methadone. Key parts of the family history that should raise concern for a patient potentially having undiagnosed congenital LQTS include a family history of prolonged QT syndrome, sudden cardiac death, unexplained drowning, nonalcohol-related driving fatalities, and sudden infant death syndrome. Although genetic testing exists for genes known to contribute to congenital LQTS, screening family members of patients with known LQTS is controversial as only up to 75% of patients with congenital LQTS have a detectable genetic mutation and the extent of penetrance varies allowing for some individuals with a detectable genetic mutation to never develop LQTS.[86]

Physical examination findings that suggest possible negative outcomes for patients on methadone include signs of liver disease, kidney disease, or cardiovascular disease. Before prescribing methadone, patients need to have a comprehensive metabolic panel performed as well as a measurement of the serum magnesium level to exclude the presence of kidney disease, liver disease, and electrolyte disturbances, such as hypokalemia, hypomagnesaemia, or hypocalcemia, which increase the risk of prolonged QT and TdP during methadone treatment.

Routine use of ECG as a screening and follow-up tool for methadone-induced QT prolongation is still somewhat controversial. While some authors recommend ECG screening of all patients before the start of methadone treatment and upon reaching a stable dosage,[66] others found this to be unwarranted and considered it a barrier to methadone treatment. These authors recommend ECG screening be reserved for patients with multiple risk factors for TdP [87] and for those receiving high doses of methadone (more than 100 mg daily).[32],[33],[64],[69],[76] Considering the dramatic upsurge of the medical use of methadone since 1997 and in an effort to resolve the controversy of methadone usage and QT prolongation, a multidisciplinary expert panel was formed with the objective to synthesize the available evidence regarding the effect of methadone on QT prolongation and to formulate a set of clinical guidelines regarding cardiac safety and necessary screening tests while patients are on methadone. The result of this effort was a five-step approach to

address methadone use in patients, which was published in 2009 but is not currently considered to be a guideline.[88] The consensus document developed by this panel includes the recommendation that all providers discuss the potential adverse effects of methadone, including QT prolongation and possible development of TdP, with patients before prescribing methadone. Providers are encouraged to evaluate each patient's clinical history for cardiac disease or possibly undiagnosed congenital QT prolongation. It is recommended that an ECG be obtained before initiation of methadone and repeated at 30 days and then annually to evaluate the QT interval as well as if the methadone dose >100 mg/day or if the patient experiences unexplained seizures or syncopal events. For patients with QTc between 450 and 500 ms, the potential risk for the development of further QT prolongation and possible development of TdP needs to be readdressed, and providers need to discuss the risk–benefit ratio of continuing methadone with the patient. For patients with QTc >500 ms, providers need to either reduce the dose of methadone or consider discontinuing methadone. Efforts need to be taken to mitigate further prolongation of the QT interval by eliminating any concurrent medications that may also prolong the QT interval as well as reevaluate the patient for electrolyte imbalances that may be contributing to the prolonged QT interval.[89]

Implications for the palliative care and opioid rehabilitation populations

Methadone plays a significant role in palliative care medicine for symptom control as it is a relatively inexpensive, effective, and safe analgesic. Should methadone be withdrawn from the market, the repercussions would be catastrophic. Fortunately, removal of methadone as an analgesic alternative appears to be unlikely given the infrequency of the development of TdP. The true mortality risk of QT prolongation by methadone usage is unknown.

A future option that may be considered is employing the racemic R-methadone enantiomer rather than the S-methadone enantiomer, which is currently in use in the US. In contrast to S-methadone, R-methadone has a lower blockade effect on the delayed rectifier potassium channels in Phase 3 of the AP and thus a lower risk of causing QT prolongation. R-methadone is available for medical use in Europe, but it is not yet approved for use in the United States.[80] Because of the extensive use of methadone in palliative care medicine and opioid abuse rehabilitation programs, health-care providers need to be aware of methadone's pharmacokinetics and weigh the risk–benefit ratio for each patient. Guidelines regarding risk factor elimination and ECG screening need to be further developed. The use of methadone in a patient with a poor prognosis may be justified as long as the provider has documented discussions with the patient about the potential for methadone to cause QT prolongation and the possible outcome of TdP, steps have been taken to mitigate the development of QT prolongation, and the patient's QT interval is monitored regularly for the development of prolonged QT interval. For a patient who develops TdP or significant QT prolongation while receiving methadone for intractable chronic pain that has failed to be controlled by other analgesics, discontinuation of methadone may be difficult. In such patients, placement of an automated implantable cardioverter-defibrillator may be considered for primary and secondary prevention.[90] Again, this decision would need to be made based on the patient's prognosis, risk factors, and the patient's wishes. For patients entering opioids abuse rehabilitation therapy who have known or suspected congenital QT prolongation syndrome, methadone needs to be avoided in the therapy due to the increased risk in further QT prolongation and induction of potentially fatal TdP in these individuals.

Conclusion

Methadone plays a significant role in palliative care and in opioid abuse rehabilitation programs by controlling chronic intractable pain and assisting patients to detox while mitigating the effects of withdrawal from opioid abuse as it is relatively inexpensive, is an effective long-acting analgesic that patients are less likely to develop a tolerance to, and is less likely to cause the side effects of constipation, nausea, or vomiting that are common with other analgesic medications. With the expanding use of methadone, more reports of its effects on the QT interval and development of TdP have emerged. While the QT prolongation effect of methadone has been demonstrated to be dose related in multiple studies, its actual incidence in clinical practice remains rare and typically is limited to patients with multiple risk factors for QT prolongation and to patients who receive methadone doses more than 120 mg/day.

Medical providers need to be aware of the potential for methadone to induce QT prolongation and possibly lead to fatal TdP. Evaluating patients for QT prolongation risk factors before prescribing methadone, monitoring the QT interval during treatment, and avoiding concurrent use of other medications that may lead to accumulation of methadone in the body or may contribute to QT prolongation are paramount to the mitigation of developing potentially fatal cardiac arrhythmias secondary to methadone use.

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Conflicts of interest

There are no conflicts of interest.

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Figures

[Figure 1]

Tables

[Table 1], [Table 2], [Table 3]

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