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JACC STATE-OF-THE-ART REVIEW

Cardiovascular Complications of Opioid Use

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ABSTRACT

Opioids are the most potent of all analgesics. Although traditionally used solely for acute self-limited conditions and palliation of severe cancer-associated pain, a movement to promote subjective pain (scale, 0 to 10) to the status of a "fifth vital sign" bolstered widespread prescribing for chronic, noncancer pain. This, coupled with rising misuse, initiated a surge in unintentional deaths, increased drug-associated acute coronary syndrome, and endocarditis. In response, the American College of Cardiology issued a call to action for cardiovascular care teams. Opioid toxicity is primarily mediated via potent μ-receptor agonism resulting in ventilatory depression. However, both overdose and opioid withdrawal can trigger major adverse cardiovascular events resulting from hemodynamic, vascular, and proarrhythmic/electrophysiological consequences. Although natural opioid analogues are devoid of repolarization effects, synthetic agents may be proarrhythmic. This perspective explores cardiovascular consequences of opioids, the contributions of off-target electrophysiologic properties to mortality, and provides practical safety recommendations.

Opioid analgesics are derived from *Papaver somniferum*, Latin for "sleep-bringing poppy." Although initially described in 2100 BCE in Sumeria (1), the first therapeutic use of opium was in London in 1784 for post-operative analgesia (2). The term *opiate* refers to substances naturally derived from the poppy that bind opioid receptors, whereas *opioid* refers to any compound—natural, semisynthetic, or synthetic—that binds to opioid receptors. Opium is the crude isolate and contains codeine, thebaine, and morphine. Manufactured in 1806, morphine was named after the ancient Greek god of dreams, Morpheus (3) and is currently the standard by which potency is graded within the opioid class. In 1874, a putatively less addictive agent, diacetylmorphine, also known as heroin, was synthesized. Although a natural derivative, it was paradoxically more potent than morphine because of its decreased polarity, facilitating rapid penetration of the blood-brain barrier. As an over-the-counter drug in the United States, heroin kindled the first opioid epidemic in the late 1800s, particularly among rural women; in the 1970s, a second, intravenous heroin epidemic ensued, predominantly

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AP = ventricular action potential

CAD = coronary artery disease

CI = confidence interval

C_{max} = maximum serum concentration

CNS = central nervous system

ECG = electrocardiographic

FDA = U.S. Food and Drug Administration

hERG = human cardiac Ether-à-go-go-related gene

IC_{50} = 50% in vitro inhibitory concentration

IDU = injection drug user

I_{K1} = the inwardly rectifying potassium current

I_{Kr} = the delayed-rectifier potassium ion current

LAAM = levacetalymethadol

MI = myocardial infarction

OR = odds ratio

NOP = nociceptin/orphanin FQ peptide

PRR = promotional reporting ratio

QTVI = QT Variability Index

afflicting men in metropolitan areas (4). Subsequently, a third opioid epidemic commenced in the early 1990s. It was by far the most lethal and primarily resulted from long-acting synthetic opioids prescribed for chronic, noncancer pain.

In 2020, the American College of Cardiology issued a Call to Action, noting that cardiovascular medicine and surgery care teams were not untouched by this national epidemic; acute coronary syndrome (ACS) admissions as a result of drug abuse increased from 168 to 315 per 100,000 quarterly in 2015 despite a decrease in overall ACS admissions; endocarditis cases nearly doubled from 2010 to 2015 (5). From 1999 to 2018, a staggering 450,000 unintentional deaths occurred in the United States, primarily attributed to prescription opioids (6). The pharmaceutical industry potentially fanned the flames of this epidemic. The U.S. Drug Enforcement Administration expressed concern, for instance, that OxyContin (Purdue, Stamford, Connecticut) was aggressively promoted to inadequately trained physicians, increasing abuse and diversion. Marketing included patient starter coupons for free opioids, web advertisements, and the provision of fishing hats, stuffed plush toys, coffee mugs with heat-activated messages, and music compact discs for prescribers (7).

The clinical focus during this crisis has largely been directed toward prescriber behavior within the primary care, pain management, and addiction medicine fields, aimed at reducing the risk of overdose and resultant ventilatory depression. However, cardiovascular specialists are increasingly affected, given growing evidence that opioids may trigger both cardiovascular events and life-threatening arrhythmias. The latter largely reflects torsade de pointes, a form of polymorphic ventricular tachycardia with obligatory QT-prolongation. Although the archetypical proarrhythmic drug category is Vaughn William class III antiarrhythmics, keen clinical observation and postmarketing surveillance have unearthed a litany of non-antiarrhythmic drug-associated ventricular tachycardia, including many prescription and even over-the-counter opioids. Here, the cardiovascular consequences of chronic opioid use, misuse, overdose, and withdrawal are explored, with an emphasis on emerging evidence for ancillary cardiac repolarization effects of synthetic analogues.

HIGHLIGHTS

- Opioid overdose is a leading cause of unintended mortality; receptor-mediated versus off-target effects may help distinguish cause of death.
- Both opioid agonism and antagonism/withdrawal are associated with adverse cardiovascular events.
- Synthetic opioids, including forms available over the counter, can be proarrhythmic.
- Risk mitigation strategies are needed to address ventilatory depression, ventricular arrhythmia, and the rising incidence of endocarditis.

OPIOID RECEPTOR-MEDIATED CARDIOVASCULAR CONSEQUENCES

OPIOID RECEPTOR FUNCTION. The effect of narcotic analgesics on the cardiovascular system is primarily attributable to on-target opioid receptor–mediated effects and only secondarily through unexpected off-target receptor properties. The mu (μ), kappa (κ), delta (δ) and nociceptin/orphanin FQ peptide (NOP) receptors constitute the traditional pharmacodynamic system. Although classified into many subtypes ($\mu_{1\text{-}3}$, $k_{1a,b;2a,b;3}$; and $\delta_{1,2}$), they are all G protein coupled, forming dimeric complexes, which signal kinase cascades, effectuating a variety of protein changes (8) that affect diverse physiologic functions ranging from immunity to feeding, obesity, and resultant hyperglycemia (9). Well-recognized manifestations include analgesia, euphoria, ventilatory depression, constipation, and pruritus, all modulated through central and peripheral μ-receptor activation. This pathway is exploited clinically for a number of U.S. Food and Drug Administration (FDA)–approved indications, including prescription analgesics (e.g., oxycodone), over-the-counter antitussives (e.g., dextromethorphan), and over-the-counter remedies for diarrhea (e.g., loperamide).

Despite these established effects, opioid-receptor modulation is increasingly recognized to affect the cardiovascular system because endogenous opioid peptides, including endorphins, enkephalins, and dynorphins, are also present in the human heart (9). Outside the central nervous system (CNS), opioid receptor functions include the modulation of heart rate, inotropic state, vascular function, and cellular

adaptation to ischemic injury. Although both δ and κ receptors are abundant on ventricular myocytes, cardioprotective effects appear to be preferentially mediated via activation of δ-receptors in humans (10).

CARDIOVASCULAR COMPLICATIONS OF OPIOID USE, MISUSE, OVERDOSE, AND WITHDRAWAL

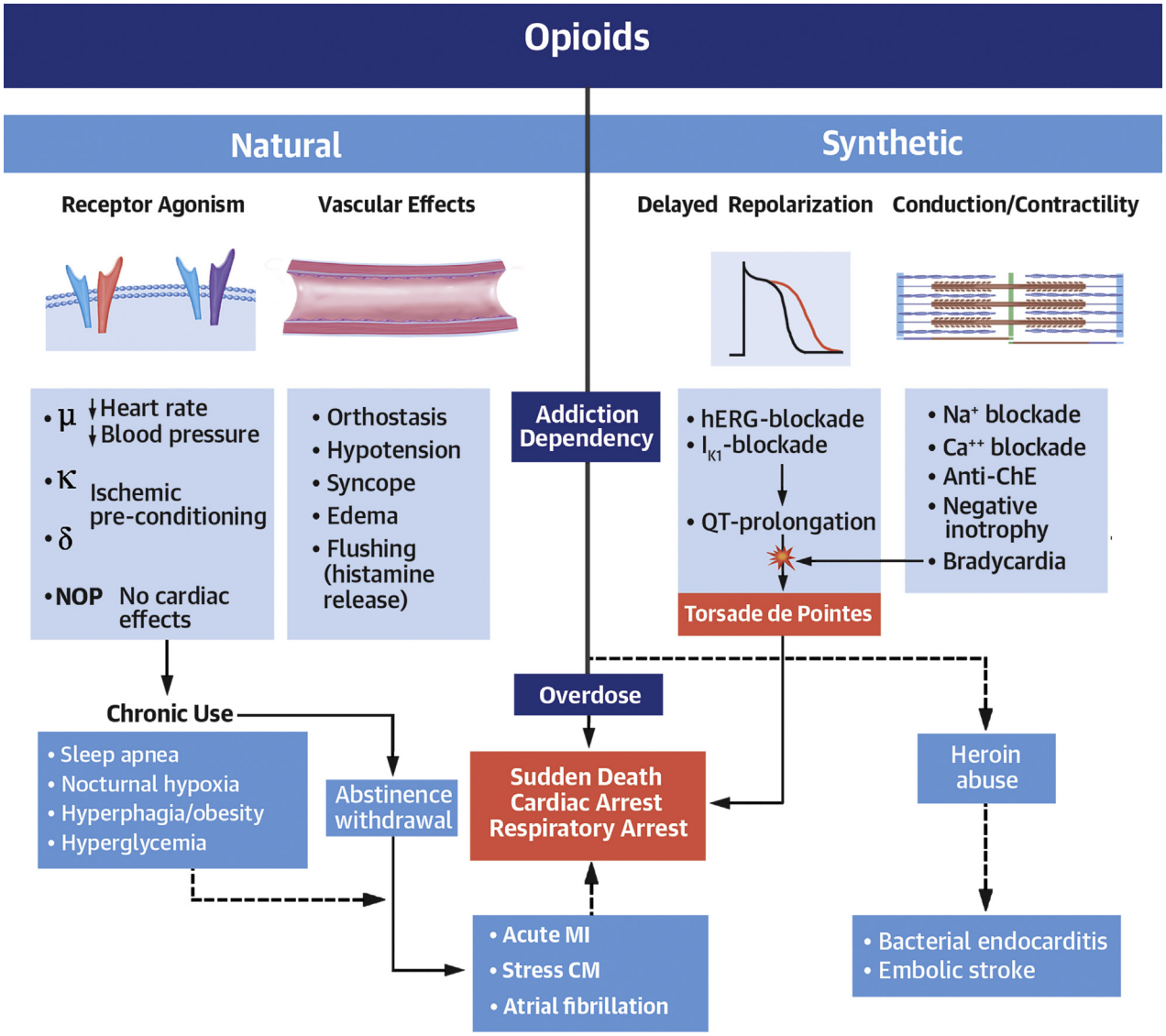
ACUTE CARDIOVASCULAR IMPACT OF OPIOID AGONISTS. Effects of opioid receptor agonism on the cardiovascular system are multifactorial and highly dependent on the circumstances of patient exposure. Chronic opioid use, misuse, overdose, and withdrawal are each associated with unique complications including vascular, valvular, and arrhythmic sequelae. By contrast, acute opioid receptor-mediated cardiovascular effects are well known and include hypotension, orthostasis, syncope, and bradycardia. Hypotension is primarily mediated through μ-receptor vasodilatation, which is consequently linked with common adverse events such as peripheral edema, flushing, and palpitations. In the United States, opioids such as morphine are ubiquitously used in the ACS setting, given its vasodilatory properties with reduction in preload, which may reflect augmentation of vasodilatory peptides, including atrial natriuretic factor (11). However, among a cohort of 57,039 patients, morphine administered within 24 h of presentation was associated with a higher adjusted risk of death (odds ratio [OR]: 1.48; 95% confidence interval [CI]: 1.33 to 1.64) and was deleterious relative to those receiving nitroglycerin alone (12). At a minimum, it is prudent to delay the use of opioids for the purpose of suppressing chest pain until a definitive diagnosis has been established and a final treatment plan determined. A conceptual model illustrating the cardiovascular consequences of opioid use, misuse, overdose, and withdrawal is shown in the **Central Illustration** and provides a framework for addressing opioid safety in cardiology practice.

IMPACT OF CHRONIC OPIOID USE ON CARDIOVASCULAR DISEASE. The cardiovascular effects of chronic opioid use are an area of ongoing investigation. Only 1 forensic study suggested a potential benefit: 98 decedents on chronic opioid treatment were matched with 97 opioid-free decedents, and severe coronary artery disease (CAD) was found less often in methadone/opioid-positive patients (adjusted OR: 0.43; 95% CI: 0.20 to 0.94) (13). Although this study was purely associative, it bolstered the notion that opioid-dependent patients may not experience accelerated atherosclerosis akin to their cocaine-addicted counterparts (14).

One nested case-control study using the UK General Practice Research Database found an increase in myocardial infarction (MI) among 1.7 million opioid users (1.28-fold; 95% CI: 1.19 to 1.37) compared with nonusers (15), and a subsequent study found no association with CAD (16). By contrast, a substantially larger retrospective claims analysis assessed incidence rate ratios for MI and coronary revascularization among 148,657 individuals taking chronic opioids, 122,810 on chronic cyclooxygenase-2 inhibitors, and 148,657 age- and sex-matched controls not receiving analgesics (17). After adjustment, a significantly increased risk for MI/coronary revascularization, among both the opioid and cyclooxygenase-2 inhibitor groups, was shown. These data strike a cautionary note for cardiovascular specialists: limiting long-term nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease is well established, yet the same admonition may apply to chronic opioids. Notably, existing reports regarding differential consequences of opioids in acute and chronic CAD are entirely observational, which limits causal inferences. Future prospective evaluations, including nested substudies in clinical trials, are needed. Overall, available clinical evidence does not support cardioprotective effects of opioids.

CARDIOVASCULAR EFFECTS OF OPIOID OVERDOSE. Although the impact of chronic opioid use on cardiovascular adverse events remains uncertain, the connection with overdose appears more consistent. Noncardiogenic pulmonary edema from overdose has been observed for half a century (18), and in the emergent setting, hypotension and bradycardia are rapidly reversed by intravenous naloxone (9). A study of 430,459 patients hospitalized with opioid overdose found an association with ischemic events, heart failure, and arrhythmias (19). The cardiovascular event composite included acute heart failure (n = 3,074), arrhythmia (n = 22,444), stroke (n = 3,153), ST-segment elevation MI (n = 297), and non-ST-segment elevation MI (n = 10,963). Overall, these events portended substantially higher mortality (OR: 4.55; 95% CI: 4.11 to 5.04). To our knowledge, however, no study to date has demonstrated a clear association between chronic opioid use and ischemic stroke. A prospective cohort study of 29,025 participants confirmed an increased risk of cardiovascular death (adjusted hazard ratio: 1.24; 95% CI: 1.00 to 1.53) but not

CENTRAL ILLUSTRATION **Mechanistic Framework for Cardiovascular Complications of Opioids**



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Opioids result in a number of life-threatening complications, particularly in the setting of overdose and withdrawal; however, emerging evidence suggests that regular chronic use may be cardiotoxic. These complications are mediated predominantly via μ-opioid receptors, although off-target effects on cardiac conduction, contractility, and repolarization are increasingly recognized. ChE = cholinesterase; CM = cardiomyopathy.

ischemic stroke (adjusted hazard ratio: 1.04; 95% CI: 0.78 to 1.38]) (20). We speculate that autoregulation preserves cerebral blood flow during hypoxia and hemodynamic alterations in acute overdose, while these alterations may nevertheless drive demand ischemia, leading to elevations in high-sensitivity cardiac biomarkers.

CARDIAC COMPLICATIONS OF OPIOID MISUSE. One of the most important sequelae from opioid misuse is valvular endocarditis among injection drug users (IDUs) due to particulate contamination, which leads to blood-borne bacterial and occasionally fungal infection. The rising incidence of intravenous heroin abuse has resulted in a dramatic absolute increase

(+20.3%; 95% CI: 10.5 to 30.9) in cardioembolic stroke from endocarditis (21). Moreover, endocarditis in IDU patients is strongly associated with repeated prosthetic valve infections, which create ethical and societal challenges for cardiovascular disease specialists, particularly surgeons (5). A recent study found that the rate of bacterial endocarditis nearly doubled (from 15.2% to 29.1%) over a 5-year period during the opioid epidemic (22) and suggests that this catastrophic complication of opioid misuse will remain a challenge in the foreseeable future. Because the portal of entry is via peripheral veins, endocarditis among IDUs often involves right-sided valves. In the aforementioned study, *Staphylococcus aureus* was the most commonly identified pathogen among IDUs and was associated with a more virulent course (22). The ongoing opioid epidemic is likely to perpetuate these catastrophic infectious complications.

ACUTE OPIOID WITHDRAWAL AND MAJOR ADVERSE CARDIAC EVENTS. The timing and severity of opioid withdrawal relates principally to drug half-life. Heroin is short acting, and withdrawal typically begins 8 h after the last dose, subsiding in 3 to 5 days. By contrast, methadone is long-acting, and withdrawal commences 48 h after the last dose, gradually subsiding over months. The cardiovascular manifestations of opioid withdrawal are essentially opposite to those of opioid intoxication, representing a manifestation of increased catecholaminergic tone with abrupt increases in the rate-pressure product and myocardial oxygen consumption (23). This has the potential to destabilize high-risk patients, particularly those with tenuous coronary arterial perfusion from high-grade epicardial CAD, severely stenotic valvular heart disease, and significant left ventricular systolic dysfunction.

In addition, stress-induced cardiomyopathy has been described during opioid withdrawal (23), and acute pulmonary edema secondary to the opioid antagonist, naloxone, has also been described (24). Analogously, the primary mechanism for both pulmonary edema and stress cardiomyopathy is thought to reflect a rapid, unrestricted catecholamine surge. In support of this concept, the administration of intravenous naloxone augments ischemic ST-segment changes and angina during intracoronary balloon inflation (25).

This potential for acute reversal of opioid intoxication to cause cardiovascular events has attracted regulatory attention. A trial of alvimopan, a peripheral μ-opioid receptor antagonist, was performed in 805 patients randomized 2:1 to drug versus placebo and found 11 ischemic events with treatment and none with placebo, which led to a boxed warning label (26). Despite these concerns, adequately powered randomized trials to assess cardiac events with other opioid antagonists have not been conducted. Moreover, international post-marketing data evaluated oral naloxone, with and without synthetic opioids, and among 14,827,374 reports found no disproportionate signal of adverse cardiac events associated with opioid-antagonists (27).

EPIDEMIOLOGY OF THE OPIOID-ASSOCIATED MORTALITY EPIDEMIC

Although heroin abuse continues to rise in the United States, its use has been eclipsed by prescription opioids. Drug overdose, primarily from long-acting formulations, is now a leading cause of accidental death, second only to motor vehicle accidents (28,29). According to the Centers for Disease Control and Prevention, nearly half a million people died from prescription and illicit opioids from 1999 to 2018 (6), exceeding the number of U.S. soldiers killed in World Wars I and II combined. In 2014, Americans filled nearly 250 million opioid prescriptions, making them the most frequently prescribed medication class, corresponding with nearly 29,000 unintentional deaths and equating to 79 deaths/day (6). In 2018, prescription opioid-related deaths decreased yet still exceeded 15,000, suggesting an ongoing public health priority (6).

Mortality has generally been attributed to ventilatory depression from overdose, a reflection of potent μ-receptor brainstem effects. More recently, however, the contribution of arrhythmia to mortality has been recognized. A recent national study of opioid use among 857,283 U.S. veterans found a significant increase in atrial fibrillation in those receiving chronic opioids (OR: 1.34; 95% CI: 1.23 to 1.45) (30). We suspect that opioid-associated hypoventilation and central sleep apnea with nocturnal hypoxia could account for this association (**Central Illustration**). The impact of opioids and atrial arrhythmias, however, on the risk of sudden death has not been described, to our knowledge.

By contrast, ventricular arrhythmias associated with opioids have been more comprehensively assessed. Extended-release oxycodone and methadone are disproportionately implicated in opioid-associated mortality (28). Although oxycodone is the leading culprit, the death rate from methadone relative to prescription volume is an order of magnitude higher. Thus, although opioid mortality is generally commensurate with prescription volume,

methadone illustrates a unique circumstance, where toxicity reflects a confluence of potency, long half-life, and an unanticipated risk of torsade de pointes (31). Methadone, its derivative levacetalymethadol (LAAM), and buprenorphine are synthetic agents that block the human cardiac Ether-à-go-go-related gene (hERG) channel, which encodes the delayed-rectifier potassium ion current (I_{Kr}) (32). By contrast, oxycodone is a semisynthetic drug with minimal hERG blockade (33). Accordingly, methadone and LAAM cause clinically relevant QTc prolongation and torsade de pointes (34,35), whereas oxycodone does not. Indeed, the structure of oxycodone, along with natural opioids, is too rigidly constrained to intercalate within the distal hERG channel. By contrast, the 2 hydrophobic aromatic rings within methadone, LAAM, and propoxyphene are appended to a conformationally flexible molecular framework capable of hERG-blockade (**Figure 1**).

A critical electrophysiologic distinction has therefore emerged between natural and synthetic opioids. Naturally occurring compounds such as morphine are neither hERG inhibitors nor proarrhythmic, wheras synthetic opioids such as methadone are associated with sudden cardiac death (36). The ionic mechanisms, arrhythmia potential, and risk-mitigation strategies for this class of drugs exemplifies an emerging paradigm. Although this review highlights methadone as a proarrhythmic archetype, other prescription (LAAM, propoxyphene) and even over-the-counter opioids (dextromethorphan, loperamide) are discussed as part of this novel paradigm. A population framework for understanding differential susceptibility to the various cardiovascular consequences of opioids is emerging. Older patients with a greater burden of CAD are more highly represented with regard to ischemic complications (13–16), whereas younger patients, with chronic pain and substance abuse, are disproportionately observed with endocarditis and ventricular arrhythmia (23,31).

CLINICAL EVIDENCE FOR PROARRHYTHMIC PROPERTIES OF METHADONE

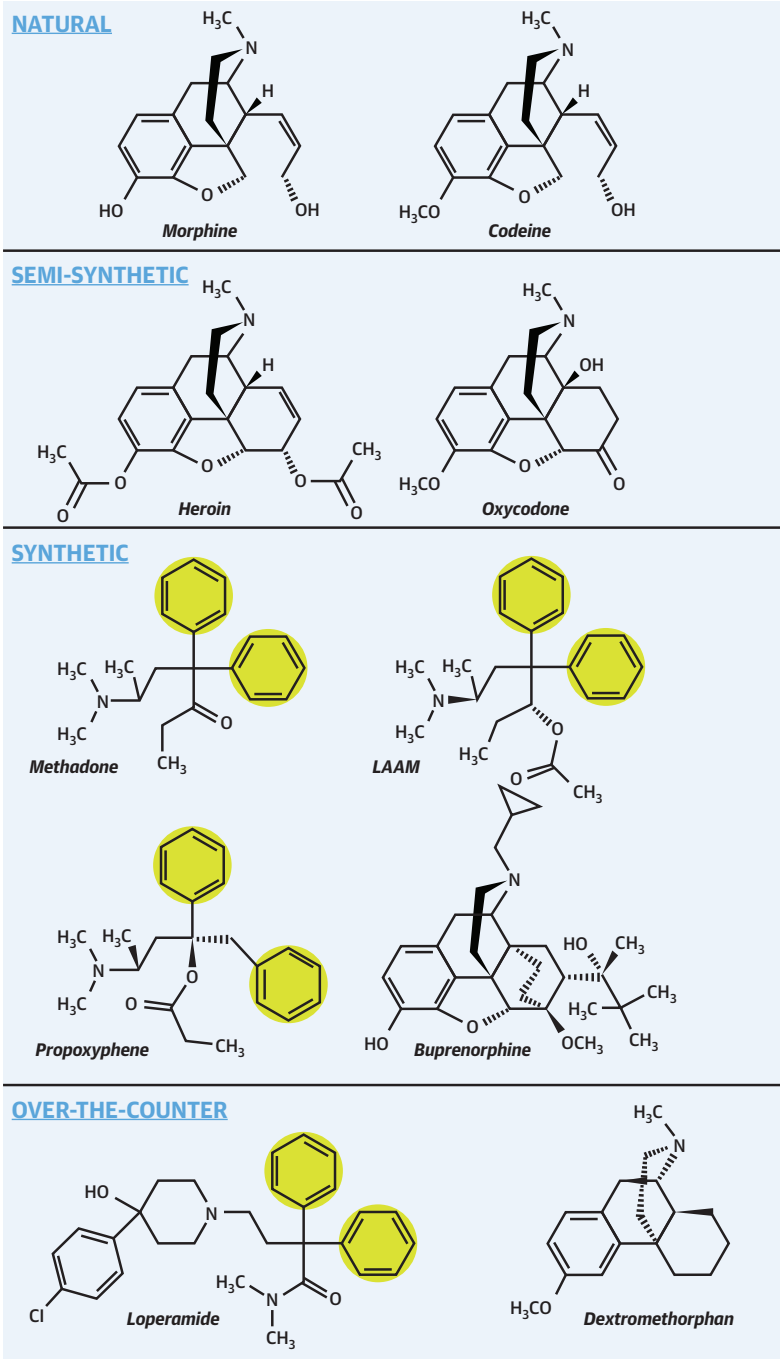
Methadone has a chemical structure that resembles propoxyphene. It was first manufactured in 1937 by German scientists and FDA approved in 1947 (37). Methadone is currently the only pure opioid agonist approved for the treatment of opioid dependency and mitigates the risk of endocarditis, hepatitis, and HIV disease. Over the past decades, however, methadone has been disproportionately implicated in opioid-related fatalities (**Figure 2**) despite representing just a small fraction of prescription volume distributed in the United States (38).

Although the reasons for the higher death rates associated with methadone cannot be reliably elucidated from observational studies, one can attribute the disproportionate mortality signal of methadone, relative to other opioids, to 4 intrinsic and extrinsic factors: 1) high potency, which is 5-fold greater than morphine; 2) prolonged elimination half-life (up to 130 h), permitting dangerous accumulation; 3) patient-related risk factors for both overdose and arrhythmia in addiction and pain populations; and 4) underappreciated liability for sudden death from ventricular arrhythmia (30,31,37).

Concern regarding sudden death associated with methadone, beyond its expected ventilatory depression, was first raised by Dr. Barry Stimmel in New York City during the 1970s heroin epidemic. Stimmel evaluated electrocardiographic (ECG) features of 75 heroin-addicted patients entering methadone treatment (39). The investigators found that QTc prolongation was nearly twice as common among patients receiving methadone compared with methadone-naive individuals. It was not until nearly 30 years later, when torsade de pointes was described in 17 patients receiving very-high-dose (mean: 397 mg/day) methadone (31). Clinical features were typical for drug-induced arrhythmia, characterized by a relative absence of structural heart disease, hypokalemia, and female predominance. Importantly, many had a methadone dose increase proximate to arrhythmia, and 2 patients who died suddenly had received substantially higher doses just 48 h before death.

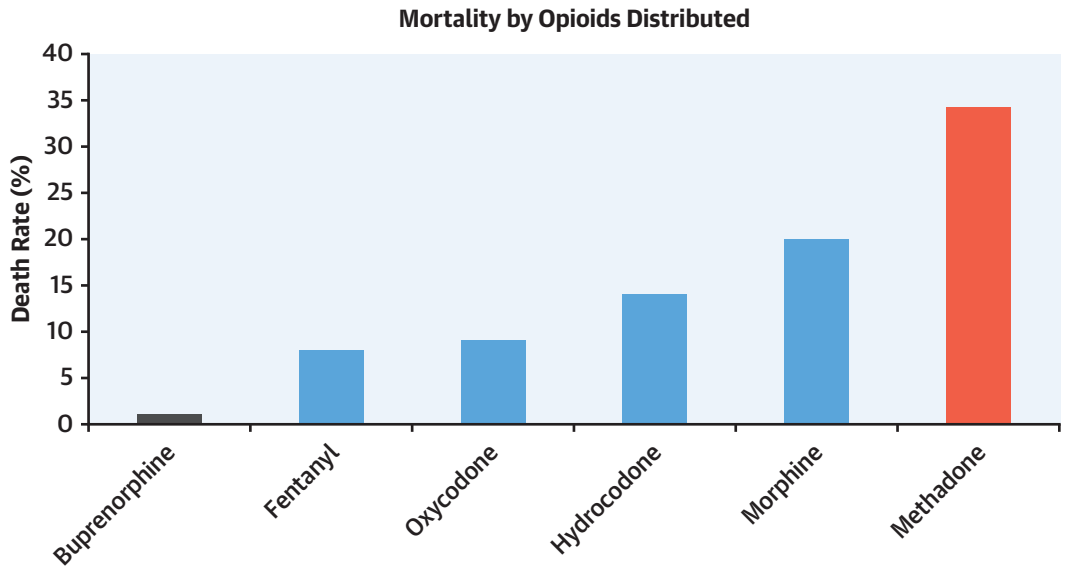
An FDA MedWatch series identified 59 methadone-associated cases of QTc prolongation/torsade de pointes, with an accompanying 8% fatality rate; again, most patients were receiving high doses (40). Another series detailed 8 individuals on high-dose (mean: 204 mg/day) methadone who received implantable cardioverter-defibrillators after aborted sudden death or torsade de pointes (41). Among those continuing methadone, torsade de pointes recurred, requiring defibrillation, whereas those who discontinued methadone did not receive device therapies. One forensic study compared 72 cases of sudden death in which methadone was detectable in postmortem blood and another 106 cases in which it was not (36). The investigators observed a striking absence of structural heart disease among deaths with modest serum methadone levels, raising the possibility that malignant arrhythmia occurred (36). This study, however, should be viewed with caution, because postmortem methadone redistribution limits inferences with respect to serum levels.

FIGURE 1 **Chemical Structures of Various Opioids and Opioid-Like Compounds**



Natural, semisynthetic, synthetic, and over-the-counter opioids (loperamide) and an opioid-like molecule (dextromethorphan). **Gold highlighting** indicates the dual aromatic rings among hERG-blocking compounds. hERG = human cardiac Ether-á-go-go-related gene; LAAM = levacetalymethadol.

FIGURE 2 Mortality Associated With Natural Semisynthetic and Synthetic Opioids Including Methadone



Signal magnitude of the disproportionate mortality of methadone relative to morphine mg equivalents distributed (107).

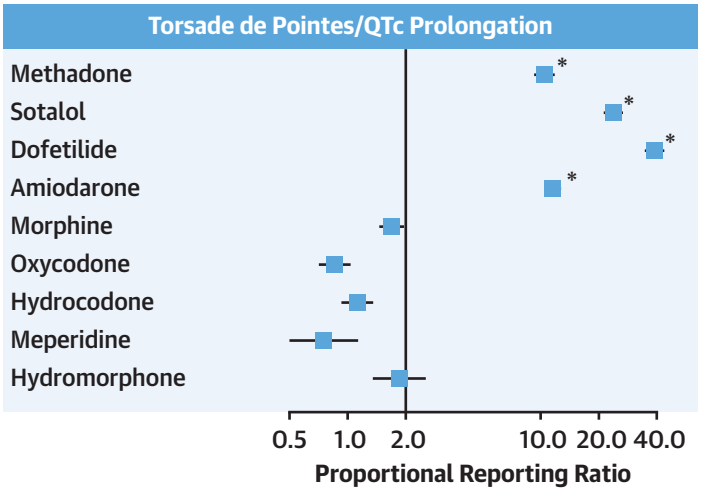
A review of FDA adverse events between 1997 and 2011 found that reports of QTc prolongation and torsade de pointes associated with methadone were commensurate with those observed for dofetilide and other established QT-prolonging agents (42). Because analysis of raw counts from spontaneous reporting databases can be biased, a proportional reporting ratio (PRR) was used to better identify disproportionate reporting. The PRR value is akin to an OR and is calculated by dividing the fraction of reports involving the reaction of interest for a given drug by the fraction of reports involving the reaction of interest for all other drugs. Generally, a PRR of >2.0 represents a valid risk signal. The PRR for methadone and QTc prolongation or torsade de pointes was 11.2 (95% CI: 10.2 to 12.4), well above the conventional significance threshold and surprisingly comparable to sotalol, amiodarone, and dofetilide (**Figure 3**). A signal was not seen, however, for the natural opioid morphine.

Since the elimination of LAAM from the market in 2013, the only 2 agonist drugs approved by the FDA are methadone and buprenorphine, creating an opportunity to evaluate comparative cardiac safety in this niche indication. From 1969 to 2011, a total of 4,418,215 adverse events were evaluated; 7,283 involved buprenorphine, and 14,915 involved methadone (43). QTc prolongation or torsade de pointes was markedly higher with methadone (n = 390 [2.6%] vs. n = 19 [0.3%]), as were PRRs for ventricular arrhythmias in general and torsade de pointes specifically (**Figure 4**).

Perhaps the most clinically applicable data regarding arrhythmia risk is gleaned from studies directly evaluating the impact of methadone on QTc. One ambulatory study of 138 patients (44) found that 16% had a QTc interval of >450 ms, a categorical risk threshold used in regulatory assessments of QTc liability (45), and 100% of patients with a prolonged QTc interval were receiving high doses (>120 mg/day). A larger cross-sectional study analyzed 393 inpatients receiving methadone and 43 on buprenorphine (46). QTc interval prolongation (>440 ms) was observed among 32% of methadone-treated patients, whereas no patient on buprenorphine had QTc prolongation. One prospective longitudinal study involved 167 new entrants into methadone maintenance therapy (34) and showed a mean QTc interval increase of 12.4 ms at 6 months, which was significantly correlated with serum concentration.

A prospective double-blind trial evaluated the impact of LAAM, methadone, and buprenorphine on the QTc interval among 165 individuals (47). QTc prolongation, defined as >470 ms in men and >490 ms in women, occurred in 0% on buprenorphine, 23% on methadone, and 28% receiving LAAM. Overall, 10% of participants receiving methadone developed QTc prolongation of >500 ms. The

FIGURE 3 Proportional Reporting Ratios of Torsade de Pointes and QTc Prolongation for Opioids and Antiarrhythmic Agents

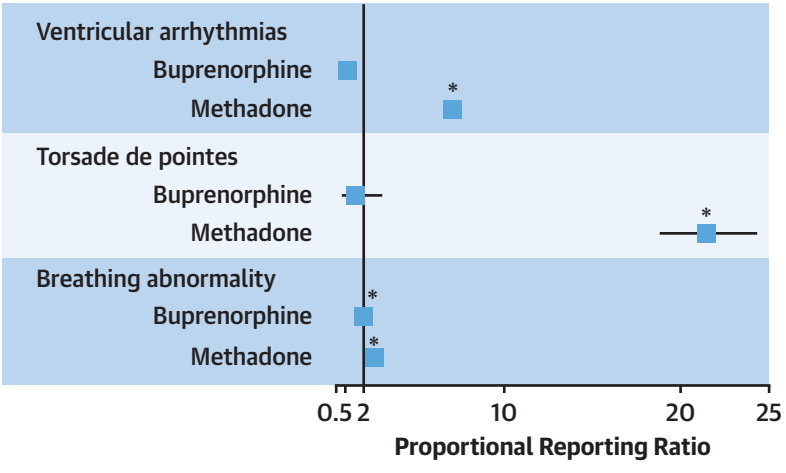


*Significant proportional reporting ratio: >2.0. The ratio (or PRR, as abbreviated in text) for methadone approaches that of antiarrhythmic drugs.

absolute changes in mean QTc at 4 weeks revealed a pharmacodynamic gradient from lowest to highest risk: buprenorphine (+6 ms, not statistically significant), methadone (+17 ms), and LAAM (+27 ms). QTc prolongation was progressive over time, with 16-week aggregate changes of +10 ms for buprenorphine, +34 ms for methadone, and +48 ms for LAAM (Figure 5A). The proportion of individuals exceeding categorical thresholds for QTc prolongation are shown at all study timepoints (Figure 5B), and as expected were highest for LAAM and methadone.

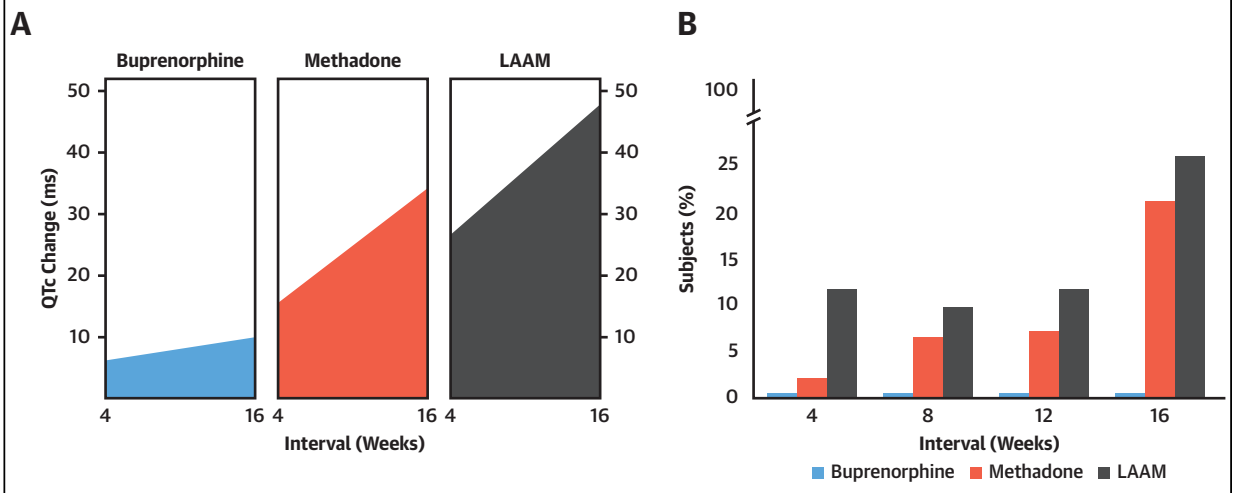
Overall, available clinical evidence supports a strong independent association between methadone and LAAM with torsade de pointes. This evidence notwithstanding, the underlying biologic mechanism of arrhythmogenesis is critical to characterizing cardiotoxicity and may augment guidelines for safe

FIGURE 4 Proportional Reporting Ratios of Ventricular Arrhythmia and Torsade de Pointes for Methadone and Buprenorphine



*Significant proportional reporting ratio: >2.0. The ratio (or PRR, as abbreviated in text) for methadone and torsade de pointes was 21-fold (95% CI: 19- to 24-fold) higher versus buprenorphine.

FIGURE 5 Risk Gradient: Temporal QTc Increase From Baseline for Synthetic Opioids in Addiction Treatment



(A) Mean QTc increase from baseline for the 3 opioids at 4- and 16-week intervals. **(B)** Categorical analysis of the proportion who develop QTc prolongation (>470 ms for men and >490 ms for women) at 4-, 8-, 12-, and 16-week intervals. LAAM = levacetalymethadol.

prescribing. In vitro experimental data, therefore, provide a useful framework for understanding opioid-associated arrhythmia while elucidating opportunities for future research.

EXPERIMENTAL MECHANISMS FOR ARRHYTHMIA RISK WITH METHADONE

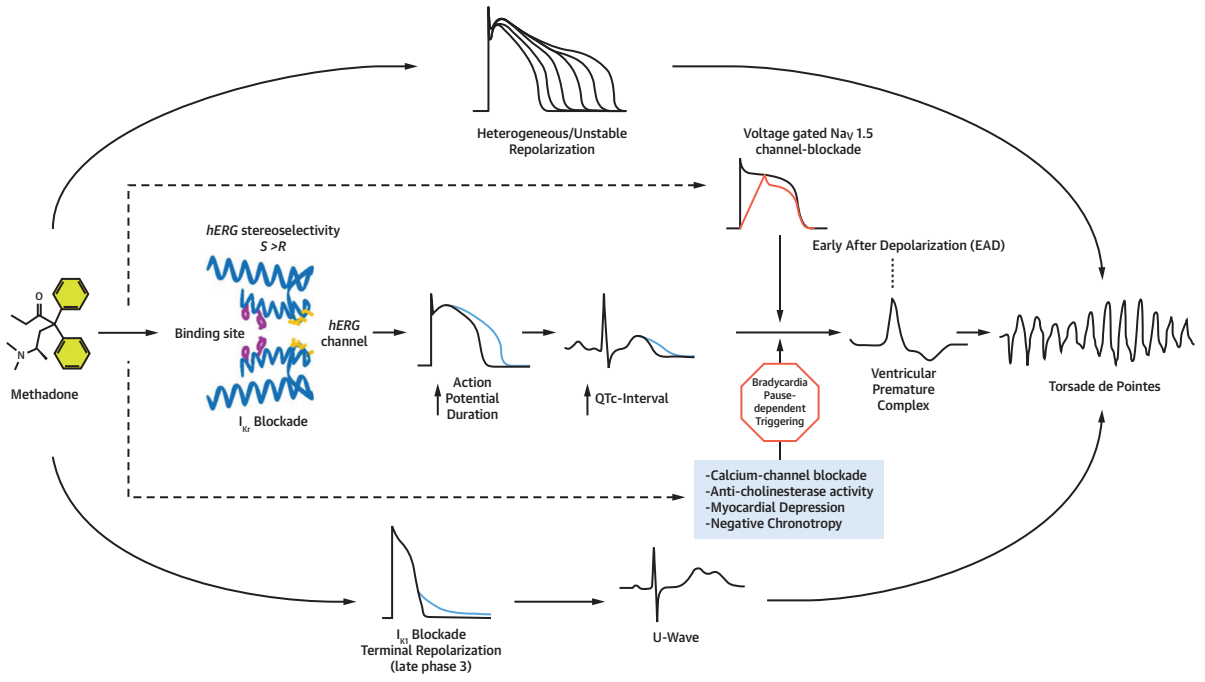
Shortly after the publication of reports of clinical arrhythmia, methadone was found to potently block I_{Kr} current (32), the most common mechanism for drug-induced QT prolongation. The proarrhythmic potential of methadone, however, is not limited solely to the aforementioned blockade of potassium channels on cardiomyocytes. Mounting evidence suggests that methadone affects cardiac contractility, chronotropy, and other ion channel physiology as well. A proposed framework for understanding its arrhythmia risk is illustrated (**Figure 6**), wherein hERG blockade figures prominently, but not exclusively, in arrhythmogenesis.

Methadone is a moderately potent I_{Kr} blocker (32), where the 2 aromatic rings occupy the distal portion of the hERG channel. Drug trapping and structure/function studies suggest that the inner cavity of the hERG channel is longer than other voltage-gated potassium channels, creating a relatively large space to accommodate drugs of diverse chemical structures (48), particularly those with 1 or more aromatic rings, such as methadone and other synthetic opioids. This hERG blockade is stereoselective: *S*-methadone is most potent, followed by the racemic mixture (*R*, *S*), and *R*-methadone is least potent (49), suggesting a gradient of cardiac safety based on chirality. The clinical applicability of this is further discussed in the "Gaps in Understanding Opioid-Associated Cardiotoxicity and Future Directions" section.

Ancillary proarrhythmic mechanisms of methadone seem likely, given relatively frequent reports of arrhythmia (42) despite only moderate hERG blockade. Recent data suggest that methadone destabilizes repolarization as measured by the QT Variability Index (QTVI) during sleep in a dose-dependent manner (50). QTVI is a measure of repolarization stability predictive of both ventricular arrhythmias and cardiovascular death. This suggests that sleep, with attendant apnea, hypoxia, and bradycardia augments the proarrhythmic impact of methadone and may serve as a triggering mechanism.

Methadone has also been associated with the development of U waves in several case reports (51,52). In one clinical study, methadone-treated subjects often exhibited U waves (11 of 24; 46%) while buprenorphine patients did not (0 of 19; 0%) (53). Although the cellular origin of U waves remains controversial, recent data from individuals with Andersen-Tawil syndrome point to at least 1 mechanism (54). These individuals have loss-of-function mutations in *KCNJ2*, the gene that encodes the inward rectifier current I_{K1}, and abnormally large U waves. The I_{K1} current regulates terminal, phase 3 repolarization in cardiomyocytes, and loss of this

FIGURE 6 **Proposed Multifactorial Mechanism for Arrhythmia Risk Associated With Methadone**



Methadone's 2 aromatic rings **(gold highlighting)** occupy the inner hERG binding site, stereoselectively blocking I_{Kr}. This delays repolarization **(blue lines)** and increases action potential duration, manifesting as QT prolongation. Phase 3 terminal repolarization (I_{K1}) blockade and increased QT variability further destabilize repolarization. Methadone blocks sodium and calcium channels and possesses anticholinesterase activity, which facilitates pause-dependent triggering of torsade de pointes.

current creates a voltage gradient after 90% repolarization of the action potential (AP), which gives rise to the U-wave. Effects of methadone on recombinant I_{K1} have been evaluated via inside-out patch clamp experiments in cells expressing Kir2.2, in whole-cell clamp of pig ventricular myocytes, and in silico using an O'Hara-Rudy ventricular model (55,56). In AP simulations, 10% I_{Kr} inhibition (free methadone concentration: 0.5 μmol/l) resulted in 6.7% prolongation of AP duration at 95% repolarization. In contrast, combined blockade (I_{K1} by 50%, I_{Kr} by 10%) caused a 2-fold greater increase in AP duration at 95% repolarization (12.4%) and additional slowing of the trajectory of terminal repolarization. In vitro I_{K1}-blockade is supported by clinical experience that methadone is associated with the development of U waves (51–53). This, coupled with modest I_{Kr} blockade, likely exerts a synergistic effect blocking both late and terminal repolarization.

Methadone also exerts both cardiac conduction and contractility effects via a local anesthetic effect mediated by sodium-channel blockade (57,58), anticholinesterase activity (59), calcium-channel blockade (60), and direct myocardial depressant and negative chronotropic effects (61). This may increase arrhythmia susceptibility by engendering bradycardia, pause-dependent early afterdepolarizations, and subsequent triggering of torsade de pointes. Methadone-associated bradycardia has been confirmed in clinical reports (62,63).

Similar to other proarrhythmic compounds, methadone-associated torsade de pointes results from a confluence of factors. Age, sex, and genetic polymorphisms in methadone metabolism (49) as well as variable expression of cardiac ion-channel activity are increasingly recognized intrinsic risk factors, whereas hypokalemia is the most common extrinsic risk factor (31). Cocaine is a frequently abused substance by opioid-dependent patients, which may synergistically trigger torsade de pointes with methadone (64). Cocaine has surprising similarities to methadone, because it exhibits both a local anesthetic effect (sodium-channel blockade) and I_{Kr} blockade (65). Moreover, antipsychotics and antidepressants may prolong the QTc interval and are often coadministered to those who develop

TABLE 1 Summary of Arrhythmia Risk Stratification for Selected Opioids

Agent	QTc Change Magnitude*	I_{Kr}-Blockade IC_{50}, μmol/l	C_{max}, μmol/l	IC_{50}/C_{max} Ratio	Intrinsic Drug Factors	Extrinsic Factors	Torsade de Pointes
LAAM	+++	2.2	1	2.2	Very potent agonist Very long $T_{1/2}$	Psychotropic and antiretroviral drugs increase QTc liability	Yes
Methadone	++	3–9.8	3.6	0.83–2.7	Multiple CYP enzymes† Na^+-channel blockade Ca^{++}-channel blockade Very potent agonist Long $T_{1/2}$	Psychotropic and antiretroviral drugs increase QTc liability	Yes
Propoxyphene	++‡	44	0.239	188	Na^+-channel blockade	Older age	Yes
Buprenorphine	+	75	36	208	Mixed μ-agonist antagonist Potent	Psychotropic and antiretroviral drugs increase QTc liability	Only with concomitant methadone
Loperamide	Overdose only	0.3	0.025	12	Na^+-channel blockade	P-glycoprotein and CYP3A4 inhibitors	Yes
Oxycodone	Overdose only	171	0.049	>3,400	–	No	No
Dextromethorphan	Overdose only	5.1	0.12	42.5	–	No	No
Codeine	None	97–300	0.66	>455	–	No	No
Morphine	None	>1,000	2.5	>400	–	No	No

*Agents ranked in descending order of risk, based on magnitude of QTc change from baseline: highest (+++: >30 ms) to lowest (+: ~10 ms). IC_{50}/C_{max} ratio is a pharmacologic safety measure where lower numbers connote higher risk, but this ratio cannot be viewed in isolation. †CYP indicates cytochrome 2D6, 2C19, 2B6, 2C8, 2C9 metabolic pathways. ‡QTc prolongation with propoxyphene in part reflects Na^+-channel blockade (increased QRS).

CYP = cytochrome; $T_{1/2}$ = pharmacologic half-life.

torsade de pointes (40,42). This "proarrhythmic polypharmacy" reflects the frequent presence of concomitant substance use associated with emotional illness and the limited options to modulate anxiety, pain, and depression among these vulnerable patients.

CARDIAC SAFETY GUIDELINES FOR MONITORING METHADONE

In an attempt to reduce methadone-associated arrhythmia, the FDA instituted a boxed warning label in 2006 (66). The U.S. Center for Substance Abuse Treatment convened a guideline committee that recommended QTc interval screening in methadone treatment (67). Due in part to skepticism in the addiction community, a Cochrane review was undertaken that concluded that QTc prolongation is not a safety concern because available evidence did not demonstrate that ECG screening reduces methadone-associated mortality (68). Given the rarity of torsade de pointes, however, no available studies conclusively demonstrated that ECG screening reduces mortality for any QTc-prolonging medication, including sotalol and dofetilide. What is clear, however, is that ECG monitoring leads to identification of QTc prolongation and treatment modification. Katz et al. (69) demonstrated that ECG screening patterned after the U.S. Center for Substance Abuse Treatment-convened guideline (67) led to a statistically significant reduction in population mean QTc interval among those with a QTc of >500 ms (69). In these patients, the QTc interval decreased significantly (−55.5 ms; 95% CI: −77.0 to −33.9; p = 0.001), and the majority dropped below the 500-ms threshold. Based on these data and other considerations, a 12-lead ECG is recommended at baseline, within 30 days, annually, and if the methadone dose exceeds 100 mg/day (67).

ADDITIONAL OPIOIDS AND ARRHYTHMIA POTENTIAL

A number of additional opioid derivatives have proarrhythmic potential that are predominantly, but not exclusively, mediated via hERG blockade akin to methadone.

LEVACETALYMETHADOL. LAAM is a long-acting methadone derivative used exclusively for opioid addiction. It is a moderately potent hERG-blocker, as assessed by the ratio of the 50% in vitro inhibitory concentration (IC_{50}) of I_{Kr} relative to the maximum serum concentration (C_{max}) (32). This IC_{50}/C_{max} ratio predicts, albeit imperfectly, the risk for torsade de pointes. The ratios for LAAM, methadone, and other opioids are depicted, along with the expected magnitude of QTc changes and ancillary arrhythmia risk factors (**Table 1**). LAAM's association with torsade de pointes (35) led to marketing discontinuation, after regulatory agencies required stringent QTc monitoring analogous to that required for sotalol (70).

BUPRENORPHINE. Unlike methadone, buprenorphine is a partial μ-agonist, δ-agonist, partial NOP agonist, and κ-antagonist. Given its partial μ-agonism, it exhibits less ventilatory depression. Administration is approved via sublingual (often with naloxone), subcutaneous, and transdermal routes. Buprenorphine is a potent hERG blocker with an IC_{50} of 7.5 μmol/l; however, the therapeutic C_{max} is only 36 nmol/l, yielding a modest IC_{50}/C_{max} ratio of 208 (32). The first description of buprenorphine's QTc effects was in 2005, when a methadone-treated patient who developed torsade de pointes was transitioned to buprenorphine while hospitalized, and the QTc normalized (71). An open-label prospective study of 50 patients confirmed that buprenorphine/naloxone alone was not associated with QTc prolongation (72); however, among the 10 patients receiving HIV antiretroviral drugs, which inhibit CYP3A4, it was associated with a 13-ms increase in QTc from baseline. A recent meta-analysis of 1,114 individuals found no QTc effect with subcutaneous buprenorphine (73), and there are no reports of torsade de pointes in FDA MedWatch (43). To date, only 1 prospective study of transdermal buprenorphine showed an independent QTc liability (+9.2 ms; 90% CI: 5.2 to 13.3 ms) (74), but this occurred at twice the approved maximal dose.

PROPOXYPHENE. Propoxyphene has weak agonist activity at G protein–coupled μ-opioid receptors and is structurally similar to methadone. It exerts significant effects on conduction (QRS) and, to a lesser extent, repolarization (QT) intervals. A prospective cohort study found an increase in mean QRS duration of about 20% compared to a group on other opioids (75), in line with a case series of 222 patients where QRS widening and ventricular arrhythmias occurred after overdose (76). One preclinical study (77) found that at clinically relevant drug concentrations, I_{Kr} is increased, whereas at higher concentrations it is reduced. Curiously, propoxyphene induced a loss of ion-channel selectivity, leading to a 30-fold increased Na^+ permeability. Propoxyphene also altered gating of hERG channels by slowing channel activation while accelerating deactivation kinetics (77).

A randomized, controlled, thorough QTc study was conducted (78).The placebo-subtracted change in QTc for 600 mg was +16.8 ms (upper 90% CI limit: 21.8) and for 900 mg was +27.9 ms (upper 90% CI limit: 35.4), both exceeding the 20-ms confidence threshold associated with substantial risk (45). Increases in QRS duration accounted for nearly 50% of the increase in QTc, where it is less certain whether QT prolongation has relevant prognostic import. Accordingly, it is instructive that there is only 1 case of torsade de pointes in the literature (79). Furthermore, no increase in risk for sudden death with propoxyphene compared to hydrocodone was observed in claims data (80). Thus, Na^+ channel blockade may mitigate its propensity to cause early afterdepolarizations, which triggers torsade de pointes. Regardless, given cases of nonpolymorphic ventricular tachycardia, propoxyphene was withdrawn from the European market in 2009 (81) and the U.S. market in 2010 (82).

OXYCODONE. One study suggests that oxycodone inhibits the hERG channel (33), but the report assessed 2 heterologous cell lines expressing human hERG channels with conflicting results. In 1 cell line, oxycodone had no effect on I_{Kr}, whereas in *Xenopus* oocytes, the IC_{50} was estimated to be 171 μmol/l, at more than 100 times the expected therapeutic level. Indeed, the structure of oxycodone is distinct from methadone, and the molecule may be too polar to lodge in the distal hERG-channel pore, as previously noted (**Figure 1**).

Clinical data relating oxycodone dose to arrhythmia are sparse. Although a dose-dependent relationship with the QTc interval was noted retrospectively (33), pre-drug QTc values and concomitant drugs were not reported. To date, only 1 study documented QT prolongation during overdose (83) but was confounded by concomitant QT-prolonging drugs. Finally, a retrospective review documented 137 oxycodone overdoses where QT prolongation was observed in one-fifth of individuals; although no arrhythmias were documented, polydrug confounding was present, and ECG adjudication was not performed (84). To our knowledge, there are no reports of oxycodone-associated torsade de pointes, which suggests minimal or no QT liability.

OVER-THE-COUNTER OPIOIDS. A number of over-the-counter synthetic opioids have the potential to prolong the QTc interval; however, regulatory standards for approval and testing are substantially different from prescription drugs. Moreover, thorough QTc studies that quantitate the impact of both therapeutic and supratherapeutic serum concentrations on repolarization are not consistently performed for these agents, and corresponding pharmacovigilance efforts are less robust.

LOPERAMIDE. Loperamide is a synthetic opioid used to treat diarrhea. The drug has been thought to present a low risk of abuse because of poor CNS penetration, given its high affinity for the P-glycoprotein pump in the blood-brain barrier. In the midst of the opioid crisis, however, reports on the dark web appeared suggesting that euphoria could be achieved with this poor man's methadone if massive doses were combined with a P-glycoprotein inhibitor such

as cimetidine (85). Unfortunately, case reports of loperamide-associated QT prolongation and cardiac arrest soon followed (86).

Near simultaneous reports from Kang et al. (87) and Klein et al. (88) revealed that loperamide is an extraordinarily potent hERG blocker, with an IC_{50} in the nanomolar range. In addition to hERG inhibition, loperamide is a Na^+-channel blocker similar to other synthetic opioids, with IC_{50} values of 297 and 239 nmol/l at holding potentials of −90 and −70 mV, respectively (87,88). As predicted, pharmacovigilance analyses from both the United States and European Union demonstrate a substantial number of ventricular arrhythmias associated with loperamide, including medically refractory torsade de pointes requiring isoproterenol overdrive (89,90).

DEXTROMETHORPHAN. The most common over-the-counter antitussive in the United States (Robitussin DM, GlaxoSmithKline, Warren, New Jersey) is a morphinan compound, approved in 1958 as a safer alternative to codeine. Dextromethorphan is the dextrorotatory isomer of the potent opioid levorphanol and binds poorly to opioid receptors (91). In the 1990s, it was known as a poor man's phencyclidine (92) and, in the setting of overdose, was associated with up to an 80-ms increase in QTc (93). Dextromethorphan inhibits I_{Kr}, with an IC_{50} of 5 μmol/l (94). Although a combination product containing dextromethorphan and quinidine sulfate was linked with torsade de pointes (95), this likely reflects effects of the quinidine component. To our knowledge, dextromethorphan as monotherapy has never been associated with arrhythmia. Nonetheless, available evidence is strikingly analogous to loperamide in that over-the-counter compounds appear to be safe when used appropriately, but supratherapeutic doses result in substantial hERG inhibition; QT prolongation; and, in the case of loperamide, torsade de pointes.

Overall, the mechanism of arrhythmogenesis for opioid compounds, either prescription or over the counter, are relatively complex and require ongoing investigation to safeguard public health. Moreover, a number of intrinsic drug factors, as well as a host of extrinsic patient-level factors, create a broader substrate for arrhythmia. Drugs discussed in this review along with contextual information to elucidate differential QT liability are shown (**Table 1**).

GAPS IN UNDERSTANDING OPIOID-ASSOCIATED CARDIOTOXICITY AND FUTURE DIRECTIONS

CHIRAL METHADONE ISOLATES. Although buprenorphine has an order of magnitude greater cardiac safety profile relative to methadone, the possibility that isolated chiral methadone molecules may substantially improve cardiac safety must be considered. Ansermot et al. (49) demonstrated a significant reduction in the QTc interval with stereoselective shifting from *S*- (accounting for the majority of hERG blockade) to *R*-methadone. Methadone use eclipses buprenorphine worldwide; at present, the vast majority receive the racemic (*R*, *S*) mixture, and pure *R*-methadone is available only in Germany.

ADDITIONAL FACTORS AFFECTING CARDIAC SAFETY. Genetic and metabolic factors remain an important area of future research to provide more tailored, individually based therapy. Common variants in *KCNH2*, which encodes the hERG channel, can significantly affect the sensitivity to drug blockade and resultant QT prolongation. A lysine codon substitution at 1 or both alleles in position 897 of *KCNH2* was found in 88% of subjects in 1 study (96). Each allele was associated with a 15-ms increase in QTc, with 2 copies resulting in a 30-ms increase compared to those with a threonine codon.

Another gap in our understanding of opioid-associated mortality relates to the proximate context in which sudden death occurs. In clinical trials, death during sleep is typically adjudicated as sudden cardiac death from malignant arrhythmia. Methadone-related fatalities occur during sleep, and this reflects, at least in part, significant ventilatory suppressing effects of potent opioids—especially when used in combination with benzodiazepines or alcohol. Although methadone shares this property with all opioid agonists, suppression of the ventilatory drive may simultaneously increase the risk for torsade de pointes if concurrent hERG blockade is present. There is an increased prevalence of central sleep apnea in methadone-treated patients when compared to body mass index-matched, non-opioid-using control individuals (97). Sleep apnea has been associated with bradycardia and QT prolongation (98) even in the absence of drugs that delay repolarization and, as previously mentioned, serves as an arrhythmia triggering mechanism. Monahan et al. (99) reported that sleep-disordered breathing confers an 18-fold higher risk for ventricular tachycardia when compared to nonobstructed breathing (99). Individuals with congenital long QT syndrome, who have a mutation in the hERG channel and reduced I_{Kr} analogous to methadone users, have an increased risk for death during sleep (100). It is therefore likely that sleep-disordered breathing and respiratory depression act synergistically with the QT-prolonging effects of synthetic opioids to increase the risk for

nocturnal sudden death. As previously noted, methadone increased QTVI during sleep (50), reaching levels consistent with those seen in individuals with heart failure, which portends an increased mortality (101). At present, it remains unclear whether the ventilatory depression associated with other opioids might result in a similar destabilization of cardiac repolarization. Opioids suppress the brain stem's sensitivity to CO_2, resulting in a tolerance to hypoxia and a significant slowing of ventilatory rate. Although these 2 toxic mechanisms may be synergistic in causing sudden death, it is clear that certain individuals are at much greater risk for death due to ventilatory suppression and others for cardiac arrhythmias (102). The patient characteristics associated with sudden death due to ventilatory depression versus those prone to cardiac arrhythmias are obviously overlapping yet may inform population-based risk mitigation strategies (**Table 2**).

TABLE 2 Comparative Risk Profiles for Ventilatory Depression and Cardiac Arrhythmia

Potential Risk Factors: Ventilatory Depression	Potential Risk Factors: Torsade de Pointes
Age >55 yrs	Female sex
Chronic lung disease	Structural cardiovascular disease
Polysubstance use (e.g., benzodiazepines)	Electrolyte derangement (e.g., hypokalemia)
Opioid-naive patients	Concurrent use of QTc-prolonging drugs
Rapid dose increases	Prolonged baseline QTc interval
Obesity and obstructive sleep apnea	Cytochrome P450 3A4 inhibitors
μ-opioid receptor agonism > hERG blockade (e.g., fentanyl)	μ-Opioid receptor agonism = hERG block (e.g., methadone)
Potent μ-agonist opioids	Synthetic opioids (methadone, LAAM)

Opioid-associated mortality is difficult to assess post-mortem but reflects overlapping influences of both ventilatory depression and delayed repolarization among synthetic analogues.
hERG = human cardiac Ether-á-go-go-related gene; LAAM = levacetalymethadol.

OPIOIDS FOR PROCEDURAL SEDATION. Finally, future outcomes studies are needed regarding the routine use of potent opioids in U.S. cardiac catheterization laboratories as part of peri-procedural sedation. Emerging data suggest that opioids such as morphine and fentanyl delay gastric absorption and reduce the effects of oral $P2Y_{12}$ platelet inhibitors like clopidogrel, ticagrelor, and prasugrel (103). This suggests that the European standard foregoing potent opioids for cardiac procedures is warranted, particularly where rapid platelet inhibition is needed. As such, the long-standing reliance on morphine and fentanyl in the setting of ACS and chronic CAD should be questioned, given emerging concerns regarding the adverse cardiovascular effects of opioids.

SUMMARY RECOMMENDATIONS

Given the totality of evidence, we contend that opioids have a very limited role in cardiovascular practice: solely in post-procedure acute pain. Opioids exhibit a myriad of cardiovascular complications including hypotension, bradycardia, peripheral vasodilatory flushing, and syncope. By contrast, opioid withdrawal triggers hypertension, tachycardia, stress cardiomyopathy, and potentially ACS. All of these physiologic manifestations are mediated via opioid receptor agonism and antagonism or withdrawal of receptor stimulation. Agonism of the μ-opioid receptor is the primary pathway mediating analgesia, euphoria, CNS depression, and drug dependency, whereas κ and δ receptors mediate ischemic preconditioning and other ancillary effects (104) not proven to benefit patients. However, it is the non-opioid receptor-mediated effects that represent a unique clinical, scientific, and safety paradigm. Specifically, although natural opioids cause ventilatory depression, synthetic opioids exhibit additional influences on conduction, repolarization, and arrhythmia risk in susceptible individuals. Clinical recommendations for reducing opioid-associated complications are shown (**Table 3**).

CONCLUSIONS

Cardiovascular complications of opioids are a major public health concern worldwide. Cardiovascular specialists should be prudent regarding the quantity prescribed for post-procedure patients and should avoid chronic prescribing. This cautious approach is supported by recent data that 1 in 10 cardiac surgery patients exhibited potentially habitual opioid use at >3 months post-operatively (105). Early recognition of the signs of dependency and withdrawal are therefore essential to ensure prompt referral to addiction treatment resources. Moreover, ECG screening in methadone treatment significantly reduces the QTc interval among those at risk for torsade de pointes (69) and is currently adopted nationally as part of cardiac safety programs in U.S. opioid treatment programs accredited by agencies such as The Joint Commission. ECG screening is also recommended in a collaborative guideline from the Heart Rhythm Society and American Pain Association for chronic pain populations (106). These guidelines, along with more prudent dosing practices, have the potential to improve care. However, the uptake of QTc monitoring remains

TABLE 3 Clinical Considerations for Improving the Safety of Opioids

Agent	ECG Contraindications	QTc Interval Monitoring	QTc Screening (Dose)	Populations To Avoid Cardiotoxicity (Product Label)	Formulation and Administration	Dose Frequency
LAAM	If QTc of >430 ms (male) or QTc of >450 ms (female) is present, LAAM should not be administered Bradycardia (<50 beats/min)	Before start Within 12 to 14 days	Periodic (not specified)	Long QT syndrome or family history Structural cardiac disease Class IA or Class III antiarrhythmic drugs	Directly observed therapy and limited take-home dosages	Do not exceed 3 times/week dosing Ventilatory depression occurs late and persists longer than analgesia
Methadone	If QTc of >500 ms in both sexes, methadone should not be administered	Before start Within 30 days Annually	Dose of >100 mg/day	Long QT syndrome or family history Class IA or Class III antiarrhythmics Cardiac hypertrophy, hypokalemia, hypomagnesemia	Directly observed therapy and limited take-home dosages	Do not exceed 2 times/day Ventilatory depression occurs late and persists longer than analgesia
Buprenorphine	If prior QTc of >500 ms in both sexes, evaluate concomitant QT-prolonging medications	No	Consider at higher doses plus CYP3A4 inhibitors	Butrans only: avoid in long QT syndrome, Class IA/III antiarrhythmics Caution: hypokalemia, ischemia, heart failure	Sublingual Subcutaneous Transdermal	Do not exceed 1 time/day Ventilatory depression mitigated by partial antagonism
Oxycodone	None	No	No	No	Limit dose/duration	Extended release products only 1 time/day
Dextromethorphan and loperamide	None (over the counter)	No	No	No	Limit bulk purchase	Do not exceed 4 doses/day
Morphine	None	No	No	No	Caution with long-acting formulations	Do not exceed 4 doses/day

ECG = electrocardiography; LAAM = levacetalymethadol.

inconsistent and is an area where cardiovascular specialists can continue to enhance patient safety. In conclusion, the most important strategy for reducing the impact of opioids on mortality is vigilant prescribing practices, yet there remains an unmet need to promptly identify cardiovascular events in overdose, prevent endocarditis, and stratify arrhythmia risk among vulnerable patients on chronic opioid therapy.

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AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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