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CARDIOVASCULAR RISK HEALTH POLICY (W. ROSAMOND, SECTION EDITOR)

Cardiovascular Risk Associated with Medical Use of Opioids and Cannabinoids: A Systematic Review

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Abstract

Purpose of Review The long-term use of opioid and cannabinoid medications to control chronic pain and treat opioid use disorders now involves a large proportion of the population in the United States. Yet, the cardiovascular risks of opioids are not well understood. This systematic review summarizes the current literature to assess the potential cardiovascular disease risks associated with opioid and cannabinoid medications.

Recent Findings The role of long-term methadone use in increasing QT interval among people receiving methadone treatment for substance use disorders is well established. Routine electrocardiogram screenings among patients receiving methadone treatment may be helpful in early identification and prevention of ventricular arrhythmias. There is limited, but credible evidence of increased risk for myocardial infarction among patients using opioid medications for chronic pain, and equivocal evidence that opioids may lead to hypotension in the short term. Further, there is no evidence indicating that opioid pain medications increase the risk of stroke or pulmonary embolism. However, the majority of the reviewed studies include limited internal and external validity due to poor confounding control, exposure misclassification, confounding by indication, small sample size, and non-generalizable special populations. We also did not find any human studies evaluating the cardiovascular effects of cannabinoids.

Summary While the effects of methadone on cardiac conduction are well known and interventions at the healthcare practice level may help prevent potential harm, more good quality research is needed to better understand cardiovascular risk associated with the use of opioids and cannabinoids.

Keywords Opioids · Cannabinoids · Cardiovascular · QT interval · Myocardial infarction · Torsades de pointes

Background

The active ingredient of opium, morphine, was first isolated more than 200 years ago, and not long afterwards, its utility for minor anesthesia and the treatment of chronic pain came to be recognized [1]. Compounded by a common belief that pain in the United States was not being managed appropriately [2], the development of partially and fully synthetic opiates led to an increase in opioid pain reliever prescriptions since the 1990s, which led to the first wave of the opioid overdose epidemic. While the first wave of the opioid epidemic was mainly due to prescription opioids, the second and third waves followed due to illicit heroin and fentanyl-related overdose deaths, respectively, that led to a national emergency declaration in 2017 [3]. As a result, the impetus of ongoing research and policy in this area has been focused on preventing opioid use disorders and overdose deaths. However, the increased use of opioid pain relievers, and methadone and buprenorphine for treatment of opioid use disorders, demand attention towards the potential undesired effects (side effects) of opioids.

Current labelling for common prescription opioids, such as OxyContin and Vicodin, include warnings of severe hypotension and relatedly, syncope. Furthermore, other studies have also noted increased incidence of Torsades de Pointes (TDP) and QT interval prolongation [4–6], which can lead to ventricular fibrillation, sudden cardiac arrest, and death. Medical

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marijuana (cannabis) or prescription cannabinoids are now also being considered as an alternative to prescription opioids, especially to treat chronic pain and associated anxiety disorders [7, 8]. Hence, in this systematic review, we examine the evidence for potential undesired effects of opioids and cannabinoids on the cardiovascular system [4] and identify limitations and gaps in the evidence base.

Methods

Data Sources

We searched PubMed for relevant studies published between January 1st, 2010 and December 31st, 2018. Using a number of "model" articles that were highly relevant to our review topic, we developed search strategies using both keyword and Medical Subject Headings (MeSH) terms, with guidance from a librarian. However, given our broad focus on cardiovascular effects, it was determined that a search strategy comprised mostly of MeSH terms, that readily index many manifestations of cardiovascular disease (CVD) into one group, would be most effective for our purposes. The final list of terms appears in the Supplementary Material.

Study Selection

References were imported into Covidence systematic review software [9], resulting in 268 records that were reviewed by two authors. Specifically, the focus of this review was recent, original investigations of the cardiovascular effects of either prescribed opioids or cannabinoids, as opposed to cardiovascular outcomes due to illicit use of prescription opioids. We also excluded opioid overdose-related studies. Further, articles were excluded if they were: published in a language other than English, reviews, case reports, commentaries, animal studies (except one relevant cannabinoids study); or non-medical use of opioids and cannabinoids, among other reasons (Fig. 1). After initial abstract screening, 97 full text articles were further reviewed for eligibility, resulting in 21 articles being selected for qualitative synthesis. Selected studies were reviewed to summarize and compare their findings (Table 1) but were also assessed for their quality with regard to selection bias and other methodological issues (Table 2).

Of the 21 studies selected, 20 report on the cardiovascular events associated with opioids and one study reports on the cardiovascular events associated with cannabinoids. A discussion of these effects follows.

Opioids and the Heart

Most prior studies have focused on conduction-related changes in the heart, especially the prolongation of the QT interval leading to TDP characterized by ventricular tachycardia. After six cases of TDP were discovered among methadone-treated individuals in Colorado, in a retrospective case series, Krantz et al. found 17 more cases of TDP among patients receiving high doses of methadone. However, it was noted that the majority of cases had predisposing factors for cardiac arrhythmia, such as the use of other drugs with known cardiovascular effects [5]. In a randomized trial of three different treatments for opioid dependence (levomethadyl, methadone, and buprenorphine), all three treatments were associated with increased mean QTc, with more diminished effects observed in those who received buprenorphine [31]. Cardiac arrest may also be a fatal consequence of opioid use, but is typically limited to the setting of drug overdose [32, 33].

Of the 20 studies that explicated the cardiovascular effects of opioids, 16 reported effects associated directly with the heart. The most common cardiovascular effects noted were (1) changes in conduction, e.g., prolongation of QT interval, ventricular arrhythmia, and atrial fibrillation ($n = 5$ studies) [15, 18••, 22••, 24, 26]; (2) ischemic events, e.g., myocardial infarction, coronary artery disease, heart failure, and need for coronary revascularization ($n = 8$ studies) [10, 12, 17, 19, 25•, 27, 28••, 29]; and (3) compensated cardiac function, e.g., hypotension or changes in systolic and diastolic blood pressure and reduction of ejection fraction ($n = 4$ studies) [13, 14, 22••, 23].

Concurrent with prior studies, three studies that we reviewed observed QT prolongation among patients receiving methadone. Anghelescu et al. recorded electrocardiograms (ECG) for 37 pediatric patients receiving methadone analgesia for cancer pain with a median treatment duration of 28 days [24]. The authors observed that compared to pre-treatment values, mean QTc was higher during treatment; however, methadone dosage was not associated with QTc changes. Post-treatment ECGS were only collected in a very small number of individuals ($n = 7$), but also showed a relative increase in QTc [24]. In another prospective study of 68 new entrants to methadone maintenance treatment, Katz et al. observed that 69% of patients had an increased QT interval post-treatment as compared to pre-treatment, while in 31% of cases, the post-treatment QT interval was lower than pre-treatment [18••]. Overall, they observed that the mean QT interval increased from 433.7 milliseconds (ms) during pre-treatment ECG to 449.2 ms post-treatment ($p < 0.0001$) [18••]. Gholami et al. observed a direct association between increasing methadone dosage with prolongation of QT interval among 201 new methadone maintenance patients without prior history of CVD ($p < 0.01$) [15]. While results from these studies are aligned with previous findings, the evidence is usually limited by small sample size, lack of confounding control, and lack of generalizability due to focus on cancer or substance use disorder patients (Table 2).

Lee et al. examined a claims-based retrospective cohort of adult breast cancer patients in Taiwan and found that

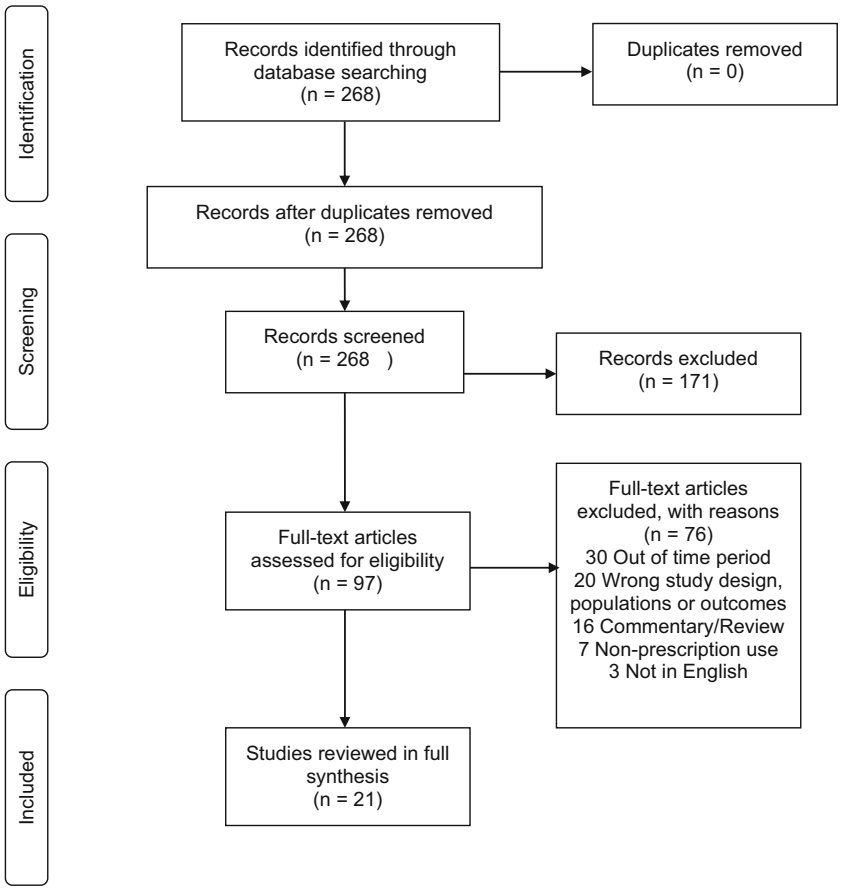

Fig. 1 PRISMA flow diagram representing identification, screening, eligibility, and inclusion of studies in the systematic review

morphine use was associated with a more than four-fold risk of atrial fibrillation compared to patients who were not treated with morphine [26]. However, patients with advanced cancers were more likely to receive morphine and also have atrial fibrillation [34] resulting in strong confounding by indication that was not addressed [26]. In another well-controlled retrospective cohort, Lentine et al. examined the association of pre-kidney transplant narcotics exposure to post-transplant cardiovascular complications [22••]. The authors found that patients with the highest level of narcotics use were almost four times as likely to have post-transplant ventricular arrhythmia and had a 43% higher likelihood of cardiac arrest compared to the lowest level of narcotics users [22••].

The reported ischemic effects of exposure to opioids include myocardial infarction (MI), coronary artery disease (CAD), heart failure (HF), and the need for coronary revascularization (CR) [10, 12, 17, 19, 25•, 27, 28••, 29]. All studies that reported ischemic events were conducted using observational study designs, including prospective and retrospective cohort studies and case-control studies, using large claims, registry-based or electronic medical records-based data that improves potential generalizability of these studies. Three studies compared opioid pain relievers to other medications that treat pain. Solomon et al. compared opioid users in a large retrospective cohort to a propensity matched cohort of patients who used non-steroidal anti-inflammatory drugs (NSAIDS) [10]. The authors found that the risk of MI, CR, and HF was elevated among opioid users as compared to NSAIDs users [HR 1.77 (95% CI 1.39–2.24)] [10]. Carman et al. compared chronic opioid users to those using cyclooxygenase-2 inhibitors and found that high cumulative doses of opioid pain medications are associated with increased risk of MI and CR following an ischemic event [12]. Ray et al. compare chronic non-cancer pain patients using opioids, including morphine, oxycodone, transdermal fentanyl, and methadone, to a propensity matched cohort of chronic non-cancer pain patients using analgesic anticonvulsants (e.g., gabapentin) and cyclic depressants (e.g., amitriptyline) [28••]. The authors found that opioid users had a higher risk of death due to cardiovascular events other than overdose as compared to patients using anticonvulsants and cyclic depressants for pain [HR 1.65 (95% CI 1.10–2.46)] [28••].

Li et al. observed that compared to no use, current opioid use was associated with a modest increase in risk of MI [OR 1.28 (95% CI 1.19–1.37)]; this association was stronger among men as compared to women and the association of opioid use with MI became stronger for both men and women with increasing numbers of opioid prescriptions [17]. In a cohort of patients with ST-elevation MI, Puymirat et al. found that patients who used pre-hospitalization morphine had

Table 1 Characteristics and key results of the reviewed studies

Author, year	Data source	Population (*N*)	Study design	Exposures (comparison groups)	Cardiovascular outcome(s)	Key CVD-related results
Cardiovascular effects of opioids						
Solomon, 2010 [10]	Claims database (Pennsylvania and New Jersey)	Medicare beneficiaries	Retrospective cohort	NSAIDS vs COX-2 inhibitors vs opioids	Myocardial infarction (MI), coronary revascularization (CR), heart failure (HF)	Risk of MI, CR, and HF was elevated among opioid users as compared to NSAIDs users [HR 1.77 (95% CI 1.39–2.24)]
Biere-Rafi, 2011 [11]	PHARMO Record Linkage System	Community-dwelling residents in the Netherlands	Case-control	Tramadol use vs no tramadol use	Pulmonary embolism (PE)	Current use of tramadol was highly associated with PE [OR 4.07 (95% CI 2.86–5.75)] compared to no use
Carman, 2011 [12]	Commercial claims database	Adults with cumulative opioids or COX-2 inhibitors ≥ 180 days	Retrospective cohort	COX-2 inhibitors vs opioids	MI, CR	Compared to COX-2 inhibitor users, those using high cumulative doses of opioids were at increased risk of MI and CR following an ischemic event
Krauss, 2011 [13]	Aeromedical transport service	EMS transports receiving ≥ 1 fentanyl bolus doses	Prospective cohort	Fentanyl vs no fentanyl	Hypotension	Hypotension was observed in only 4.9% fentanyl bolus administrations and the multivariable analyses revealed that pre-fentanyl hypotension was associated with extremely high odds of post-fentanyl hypotension (OR 30, $p < 0.001$) suggesting little role of fentanyl itself in hypotension
Qiu, 2012 [14]	11 RCTs	Women giving birth through cesarean section	Meta-analysis	Bupivacaine high dose vs low-dose bupivacaine + opioids	Hypotension	Compared to high-dose bupivacaine, the combination of low-dose bupivacaine and opioids was associated with lower incidence of maternal hypotension [RR 0.52 (95% CI 0.33–0.82)]
Gholami, 2013 [15]	Outpatient Psychiatric facility, Zurich, Switzerland	Patients on methadone maintenance treatment	Pre-post comparison	Pre-methadone ECG vs post-methadone ECG	QT interval	Direct association between increasing methadone dosage with prolongation of QT interval among new methadone maintenance patients without prior cardiovascular history ($p < 0.01$)
Lee, 2013 [16]	NHIRD, Taiwan	Prostate cancer patients	Nested case--control	Any morphine prescription before index date	Stroke	Increased risk of stroke among patients receiving morphine (compared to those not receiving morphine)
Li, 2013 [17]	The United Kingdom General Practice Research Database	Adult non-cancer patients	Nested case--control	Any opioid prescription before index date	MI	Compared to no use, current opioid use was associated with a modest increase in odds of MI [OR 1.28 (95% CI 1.19–1.37)]; stronger association with increasing number of opioid prescriptions
Katz, 2013 [18••]	Outpatient opioid treatment program	New patients in the outpatient treatment program	Prospective cohort study	Pre-methadone ECG vs post-methadone ECG	QT interval	69% of patients had an increased QT interval post-treatment as compared to pre-treatment and in 31% of cases, the post-treatment QT interval was lower than pre-treatment. Overall, the mean QT interval increased from 433.7 milliseconds (ms) during pre-treatment ECG to 449.2 ms post-treatment ($p < 0.0001$)
Lee, 2014 [19]	NHIRD, Taiwan	Cancer patients	Nested case--control	Any morphine prescription	Acute coronary syndrome (ACS)	Risk of ACS was significantly increased among cancer patients treated with morphine versus those without morphine [OR 1.32 (95% CI 1.04–1.68)]
	NHIRD, Taiwan	Cancer patients				

Table 1 (continued)

Author, year	Data source	Population (*N*)	Study design	Exposures (comparison groups)	Cardiovascular outcome(s)	Key CVD-related results
Lee, 2014 [20]			Nested case--control	Any morphine prescription within 6 months of index date	Subdural hemorrhagic stroke	Increased risk of subdural hemorrhagic stroke among patients receiving morphine (compared to those not receiving morphine)
Lee, 2015 [21]	NHIRD, Taiwan	Deep vein thrombosis patients	Nested case--control	Any morphine prescription (current vs recent vs past vs none)	Pulmonary embolism (PE)	Those who developed PE had 4.54 times the odds (95% CI 2.30–8.97) of having received morphine within the last 30 days compared to controls who did not develop PE
Lentine, 2015 [22••]	The Organ Procurement and Transplantation Network	Kidney transplant recipients	Retrospective cohort	Prescription narcotics within 1 year of transplant	Ventricular arrhythmia, cardiac arrest, hypotension	Compared to the patients with lowest levels of narcotics use, patients with the highest level of narcotics use were almost 4 times as likely to have post-transplant ventricular arrhythmia, 43% higher likelihood of cardiac arrest, and 35% increase in risk of hypotension
Goyal, 2016 [23]	Single hospital, India	Patients scheduled for elective ERCP	Randomized controlled trial (RCT)	Propofol-fentanyl (PF) regimen vs dexmedetomidine--ketamine (DK)	Hypotension	19% ($n = 8$) of PF group patients experienced hypotension compared to 0% in the DK group
Anghelescu, 2016 [24]	Pediatric oncology EMR	Pediatric cancer patients	Retrospective cohort	Methadone	QTc length	Compared to pre-treatment, mean QT interval was higher during treatment; however, methadone dosage was not associated with QT changes. Post-treatment ECGs were only collected in a very small number of individuals ($n = 7$), but also showed a relative increase in QT interval
Khodneva, 2016 [25]	The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	Adults ≥ 45 years of age	Prospective cohort	Prescription opioid use	Coronary heart disease, stroke, cardiovascular death	Prescription opioid use was not associated with coronary heart disease [adjusted HR 1.03 (95% CI 0.83–1.26)] but was associated with cardiovascular death [aHR 1.24 (95% CI 1.00–1.53)], including death from MI, stroke, heart failure, sudden death, vascular pathology, or other cardiovascular causes
Lee, 2016 [26]	NHIRD, Taiwan	Breast cancer patients	Nested case--control	Any morphine prescription	Atrial fibrillation	Morphine use was associated with a more than 4-fold risk of atrial fibrillation compared to patients who were not treated with morphine
Puymirat, 2016 [27]	The French Registry of Acute ST-elevation and non-ST elevation Myocardial Infarction	Adults admitted within 48 h of symptom onset for acute MI	Prospective cohort	Pre-hospital morphine administration	ST-elevation MI	Pre-hospitalization morphine recipients had higher odds of recurrent MI [OR 2.94 (95% CI 1.17–7.37)] but lower odds of death [OR 0.48 (95% CI 0.12, 1.85)] compared to those who did not receive pre-hospitalization morphine
Ray, 2016 [28••]	TN hospital discharge data linked with Medicaid data	Medicaid patients with a diagnosis of chronic pain within the past 90 days	Retrospective cohort	Long-acting opioids	Cardiovascular death	Opioid users had a higher risk of death due to cardiovascular events other than overdose as compared to patients using anticonvulsants and cyclic depressants for pain [HR 1.65 (1.10–2.46)]
Jobski, 2017 [29]	The German Pharmacoepidemiologic Research Database	Patients receiving extended release oxycodone-naloxone	Nested case--control	Extended release oxycodone-naloxone vs extended release high-potency opioids	MI, ischemic stroke	Risk of MI was lower among those using extended release oxycodone-naloxone compared to those using extended release opioids without naloxone

Table 1 (continued)

Author, year	Data source	Population (*N*)	Study design	Exposures (comparison groups)	Cardiovascular outcome(s)	Key CVD-related results
		or high-potency opioids				
Cardiovascular effects of cannabinoids						
Rajesh, 2010 [30••]	Animal Study	Diabetic mice	RCT	Cannabidiol	Myocardial function (ejection fraction; systolic blood pressure; diastolic blood pressure)	Compared to diabetic mice that did not receive cannabinoids, those that received cannabinoids for 11 weeks showed attenuation in diabetes-related impairment of left ventricular function, oxidative stress, and inflammation. The diabetic mice who received cannabinoids had better ejection fraction and systolic and diastolic blood pressure as compared to their counterparts who did not receive cannabinoids

Abbreviations: Non-steroidal anti-inflammatory drugs (NSAIDs); cyclooxygenase-2 (COX-2) inhibitors; propofol-fentanyl (PF); dexmedetomidine-ketamine (DK); myocardial infarction (MI); endoscopic retrograde cholangiopancreatography (ERCP); systolic blood pressure (SBP); coronary revascularization (CR); diastolic blood pressure (DBP); pulmonary embolism (PE); acute coronary syndrome (ACS); randomized controlled trial (RCT); National Health Insurance Research Database (NHIRD); Tennessee (TN); electronic medical record (EMR); emergency medical services (EMS); electrocardiogram (ECG)

higher odds of recurrent MI [OR 2.94 (95% CI 1.17–7.37)] but lower odds of death [OR 0.48 (95% CI 0.12,–1.85)] compared to those who did not use pre-hospitalization morphine [27]. Jobski et al. found that the risk of MI was lower among those using extended release oxycodone-naloxone compared to those using extended release opioids without naloxone [29].

Similarly, a population-based case-control study conducted in Taiwan also found that risk of acute coronary syndrome (ACS) was significantly increased among cancer patients treated with morphine versus those without morphine [OR 1.32 (95% CI 1.04–1.68)] [19]. However, this study was likely affected by strong confounding by indication [19]. In contrast, in 29,000 individuals of the Reasons for Geographic Differences in Stroke (REGARDS) study, Khodneva et al. found that prescription opioid use was not associated with increased incidence of coronary heart disease [adjusted HR 1.03 (95% CI 0.83–1.26)] but was associated with increased cardiovascular death [aHR 1.24 (95% CI 1.00–1.53)], including death from MI, stroke, heart failure, sudden death, vascular pathology, or other cardiovascular causes [25•]. This rigorous study included multiple methods to adjudicate and verify outcomes, including interviews with proxies and autopsy report review [25•]. Another key advantage of this analysis was its use of pill bottle review instead of patient self-report or pharmacy records to ascertain opioid use [25•].

There is mixed evidence to suggest that opioid exposure prior to and during hospitalization is associated with increased risk of hypotension. Goyal et al., in a randomized controlled trial (RCT) to examine the safety of propofol + fentanyl (compared to dexmedetomidine-ketamine) during an endoscopic retrograde cholangiopancreatography procedure, found that 19% patients who received propofol + fentanyl (8/42) had hypotension during the procedure, while there were no reports of hypotension in the dexmedetomidine-ketamine group [23]. Lentine et al. also found that patients with the highest level of narcotics use had increased risk of hypotension as compared to the lowest level of narcotics users [HR 1.35 (95% CI 1.10–1.65)] [22••]. In contrast, a meta-analysis of 11 RCTs examining the use of high-dose bupivacaine vs a combination of low-dose bupivacaine and opioids showed that the combination regimen had a lower incidence of maternal hypotension compare to high-dose bupivacaine [RR 0.52 (95% CI 0.33–0.82)] [14]. In another prospective study of fentanyl bolus dose delivery in Emergency Medical Services (EMS) helicopters, Krauss et al. observed hypotension in only 4.9% administrations [13] and the multivariable analyses revealed that pre-fentanyl hypotension was associated with extremely high odds of post-fentanyl hypotension (OR 30, $p < 0.001$) suggesting that fentanyl itself has a small role in hypotension [13]. However, this study had strong confounding by indication because the patients receiving fentanyl and transported by EMS helicopter are also more

Table 2 Methodological limitations of the reviewed studies

Author, year	Threats to internal validity					Threats to external validity	
	Strong confounding by indication	Insufficient confounder adjustment	Potential for misclassification		Potential selection bias	Small sample size	Special population
			Exposure	Outcome			
Cardiovascular effects of opioids							
Solomon, 2010 [10]			X				Older adults with osteoarthritis or rheumatoid arthritis
Biere-Rafi, 2011 [11]	X	X	X		Potential survivor bias		
Carman, 2011 [12]	X	X	X		Potential survivor bias		Individuals with private insurance
Krauss, 2011 [13]	X	X		X	Air-EMS patients in need of fentanyl administration for pain control may also be more likely to have blood loss and hence lower blood pressure	X	Patients transported by EMS helicopter
Qiu, 2012* [14]	–	–	–	–		–	Women with cesarean delivery
Gholami, 2013 [15]		X	X				Heroin-dependent methadone maintained patients
Lee, 2013 [16]	X	X	X		Potential survivor bias and patients with advanced cancers are more likely to receive morphine and to have ischemic or hemorrhagic stroke		Cancer patients
Li, 2013 [17]		X	X		Potential survivor bias		
Katz, 2013 [18••]		X	X				Patients under methadone treatment for opioid use disorders
Lee, 2014 [19]	X	X	X		Potential survivor bias and patients with advanced cancers are more likely to receive morphine and to have acute coronary syndrome		Cancer patients
Lee, 2014 [20]	X	X	X		Potential survivor bias and patients with advanced cancers are more likely to receive morphine and to have subdural hemorrhagic stroke		Cancer patients
Lee, 2015 [21]	X	X	X		Severe DVT cases are more likely to receive morphine and are also more likely to have PE		DVT patients
Lentine, 2015 [22••]					Study conducted among Medicare patients who are more likely to require kidney transplants, have cardiovascular events, and receive morphine		Kidney transplant recipients with Medicare
Goyal, 2016 [23]						X	Elective ERCP patients
Anghelescu, 2016 [24]	X	X	X		Pediatric oncology patients represent a population with worsened overall health and are more likely to receive opioids or experience ECG changes	X	Pediatric cancer patients from one hospital
Khodneva, 2016 [25]			X				Adults ≥ 45 years of age; excluding cancer and end-of-life patients
Lee, 2016 [26]	X	X	X		Potential survivor bias and individuals who may have had more advanced cancer are more likely to get morphine treatment and may also be more likely to have atrial fibrillation		Cancer patients
Puymirat, 2016 [27]		X	X				MI patients treated with pre-hospital morphine
Ray, 2016 [28••]					Potential survivor bias		Medicaid patients in Tennessee
Jobski, 2017 [29]		X					Patients receiving extended release opioids
Cardiovascular effects of cannabinoids							
Rajesh, 2010 [30••]						X	Diabetic mice

Abbreviations: Deep vein thrombosis (DVT); myocardial infarction (MI); endoscopic retrograde cholangiopancreatography (ERCP); pulmonary embolism (PE); emergency medical services (EMS); electrocardiogram (ECG) * meta-analysis of 11 RCTs

likely to be in critical conditions, including loss of blood and consequent hypotension [13].

Based on the current evidence, chronic use of opioids for pain may be associated with ischemic cardiac events, long-term methadone treatment is associated with prolongation of QT interval potentially causing ventricular arrhythmias, and there is equivocal evidence of hypotension after short-term exposure to opioids. All studies that have examined the effects of chronic opioid use on ischemic events have been based on large-scale observational data; however, only one was a well-controlled study [28••]. Other studies were often affected by strong confounding by indication, unaddressed time-varying confounding, and lacked in addressing potential exposure or outcome misclassification (Table 2). Similar and stronger limitations were observed in studies examining cardiac events related to conduction which were also extremely limited in external validity (Table 2). The evidence base on hypotension is based mainly on RCTs [22••, 23], one good quality prospective study [22••], and one prospective study with poor confounder control [13]. While the recent RCT and well-controlled prospective study suggest that use of opioids may lead to hypotension in the short term [23], synthesis from 11 other RCTs suggests the opposite [14].

Opioids and Stroke

We found five studies that examined the association between stroke and opioid medications [10, 16, 20, 25•, 29]. Solomon et al. compared opioids with NSAIDS in older adults with arthritis and found no difference between the risk of stroke among those using either of these medications [10]. Similarly, Khodneva et al. found no difference among users of prescription opioids and non-users with respect to their risk of stroke [25•]. Jobski et al. compared patients with extended release oxycodone-naloxone to those with extended release opioids only and found no difference in stroke risk among the two groups; however, they did see an increased risk of stroke with recent discontinuation or switching from opioids only to opioids-naloxone extended release medications [29]. Lastly, two studies by Lee et al. observed increased risk of hemorrhagic stroke among patients receiving morphine (compared to those not receiving opioids) in two cohorts of cancer patients [16, 20]. However, both studies were severely limited by confounding by indication because the authors did not control for type or stage of cancer—it is well understood that patients with advanced cancers are more likely to receive morphine for pain control and cancer itself is more likely to cause hemorrhagic events, leading to a spurious association between morphine prescriptions and hemorrhagic stroke [16, 20]. Hence, based on the current evidence, it seems that opioids may not be associated with stroke.

Opioids and Pulmonary Embolism

Two studies have examined the association of pulmonary embolism (PE) with opioid therapies. Biere-Rafi et al. conducted a case-control study in a Dutch population-based registry describing the association between prescription NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, and tramadol, and first incidence of PE [11]. Current use of tramadol was highly associated with PE [OR 4.07 (95% CI 2.86–5.75)] compared to no use of tramadol [11]. Lee et al. conducted a nested case-control within a cohort of deep vein thrombosis (DVT) patients in Taiwan and found that those who developed PE had 4.54 times the odds (95% CI 2.30–8.97) of having received morphine within the last 30 days [21] compared to controls who did not develop PE. However, both studies were affected by substantial confounding by indication [11, 21]. Biere-Rafi et al. did not control for many strong confounders that may lead to both tramadol use and PE, including smoking, blood pressure, body mass index, occupation, lifestyle factors, and severe trauma. They did, however, control for hospitalizations, use of anticoagulants, and use of anti-hypertensives, which could serve as proxies to address some potential confounding by indication [11]. On the other hand, Lee et al. present one of the strongest cases of confounding by indication as their sample arises from all patients already diagnosed with DVT [21]; indeed, the more severe the DVT, the more likely someone may be to receive tramadol to control pain and the more likely they are to have PE. Given the limitations of these studies, the evidence base for PE as an effect of opioids is unsubstantiated.

Cardiovascular Effects of Cannabinoids

We found only one study that examined effects of cannabinoids on the cardiovascular system in diabetes-induced mice. Rajesh et al. found that compared to diabetic mice that did not receive cannabinoids, those that received cannabinoids for 11 weeks showed attenuation in diabetes-related impairment of left ventricular function, oxidative stress, and inflammation [30••]. The diabetic mice who received cannabinoids had better ejection fractions, and systolic and diastolic blood pressure measurements as compared to their counterparts who did not receive cannabinoids [30••]. While we did not find any completed human studies on the relationship between cannabinoids and CVD at the time of our search, we found one ongoing RCT that examines the effect of tetrahydrocannabinol and cannabidiol (THC:CBD, Sativex) oromucosal spray to reduce spasticity among stroke patients [35].

Implications on Healthcare Policy and Practice

Although many new policies to combat the opioid epidemic have been enacted across the United States [36], we did not find any literature that discusses potential policy implications of the association between opioid pain relievers and CVD risk. Given the well-noted impact of methadone on QT prolongation among people receiving methadone maintenance treatment for opioid use disorders, it may be prudent to conduct routine ECG screenings to evaluate risk for arrhythmias in this population. Katz et al. determined that ECG screenings were more helpful to detect early ECG changes than prediction algorithms based on any demographic and other patient characteristics [18••]. Routine ECG screenings among methadone or even chronic opioid pain patients may hence be an important tool to address potential opioid-related CVD risk. Training and education of physicians who provide methadone maintenance or chronic pain treatment, to anticipate and mitigate cardiovascular risks by modifying methadone doses, limiting other QT prolonging medications, or considering cardiac risks from drug interactions between opioids and other medications, may be helpful in reducing adverse effects.

Conclusions and Future Directions

The studies we reviewed in this systematic review further cement the role of long-term methadone use in increasing QT interval among people receiving methadone treatment for substance use disorders. There is some evidence of increased risk for MI among patients using opioid medications for chronic pain; however, there is need of more well-controlled and generalizable studies to better characterize the association between opioid use and MI. There is equivocal evidence that opioids may lead to hypotension in the short term and there is no evidence indicating that opioid pain medications may increase the risk of stroke or pulmonary embolism. Given the large number of studies with poor confounding control and lack of measures to ensure internal validity, future studies must address these concerns to strengthen the evidence base [37••]. There is also a paucity of human studies evaluating the cardiovascular effects of cannabinoids; studies in this area will help improve clinical decision-making and the treatment of patients in need of cannabinoids, especially as more FDA-approved cannabinoids enter the market.

ECG screenings at baseline and during regular follow-up visits, as recommended by the American Pain Society and College on Problems of Drug Dependence [38••], could help physicians providing methadone maintenance treatment in preventing potential cardiovascular harms to their patients, including Torsades de pointes and other forms of ventricular arrhythmias.

Compliance with Ethical Standards

Conflict of Interest Eugenia Wong has no conflicts of interest to declare. Shabbar Ranapurwala has no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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