Circulation

AHA SCIENTIFIC STATEMENT

Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses

A Scientific Statement From the American Heart Association

ABSTRACT: Opioid overdose is the leading cause of death for Americans 25 to 64 years of age, and opioid use disorder affects >2 million Americans. The epidemiology of opioid-associated out-of-hospital cardiac arrest in the United States is changing rapidly, with exponential increases in death resulting from synthetic opioids and linear increases in heroin deaths more than offsetting modest reductions in deaths from prescription opioids. The pathophysiology of polysubstance toxidromes involving opioids, asphyxial death, and prolonged hypoxemia leading to global ischemia (cardiac arrest) differs from that of sudden cardiac arrest. People who use opioids may also develop bacteremia, central nervous system vasculitis and leukoencephalopathy, torsades de pointes, pulmonary vasculopathy, and pulmonary edema. Emergency management of opioid poisoning requires recognition by the lay public or emergency dispatchers, prompt emergency response, and effective ventilation coupled to compressions in the setting of opioid-associated out-of-hospital cardiac arrest. Effective ventilation is challenging to teach, whereas naloxone, an opioid antagonist, can be administered by emergency medical personnel, trained laypeople, and the general public with dispatcher instruction to prevent cardiac arrest. Opioid education and naloxone distributions programs have been developed to teach people who are likely to encounter a person with opioid poisoning how to administer naloxone, deliver high-quality compressions, and perform rescue breathing. Current American Heart Association recommendations call for laypeople and others who cannot reliably establish the presence of a pulse to initiate cardiopulmonary resuscitation in any individual who is unconscious and not breathing normally; if opioid overdose is suspected, naloxone should also be administered. Secondary prevention, including counseling, opioid overdose education with take-home naloxone, and medication for opioid use disorder, is important to prevent recurrent opioid overdose.

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The ongoing US opioid epidemic accounts for ≈115 deaths per day, affecting predominantly patients in the prime of adult life (25–55 years of age).[1–3] Annual US opioid-related mortality increased from 9489 to 47 600 deaths from 2001 to 2017[1,4] and is now the leading cause of death among adults 25 to 64 years of age. Opioid use disorder (OUD) affects 2 million Americans and costs an estimated $78.5 billion in annual health care expenses.[5] Added to the financial burden, an increase in cardiac arrest (CA) caused by the use of opioid medications, with or without cointoxicants and comorbidities (opioid-associated [OA] out-of-hospital CA [OHCA]), is the most dramatic manifestation of OUD.[6] OA-OHCA is distinct from other forms of OHCA with respect to pathophysiology and demographic manifestations.[7,8] However, the epidemiology and clinical profile of OA-OHCA are incompletely characterized.[9,10] This scientific statement aims to address this knowledge gap by defining unique features of OA-OHCA epidemiology, pathophysiology, and patient management that may require targeted guidelines. We also suggest that the distinct features of OA-OHCA demand a critical appraisal of education and policy decisions to improve outcomes.

HISTORICAL PERSPECTIVE

Jalal and colleagues[11] reported that the overall mortality rate from drug-related overdoses rose exponentially in the United States between 1979 and 2016 (R^2=0.99) despite variability in the specific drug use across geographic regions. The rise of the current epidemic (Figure 1)[12] is multifactorial. Contributing causes include liberal and, at times, unethical prescription practices,[13,14] underestimation of opioid addictive potential,[15–17] opioid marketing initiatives targeting prescribers,[18] research showing that pain is often undertreated,[19–21] pharmaceutical industry–supported initiatives, quality and customer satisfaction mandates, and the criminalization of nonmedical opioid use. Publications in the early to mid-1980s minimized the addictive potential of prescription opioids and the risk for increasing tolerance and required dose that correlated with adverse events.[15,16] This propagated the belief that opioids were effective and safe for treating pain, particularly chronic noncancer pain.[20,22] The American Pain Society and Institute of Medicine prioritized better assessment and treatment of pain clinically,[23] resulting in the 2000 Joint Commission pain standards identifying pain as a vital sign, raising patient expectations for adequate pain control.[24,25] As a result, the first wave of opioid prescriptions peaked in 2012 (Figure 1) at >255 million (81 prescriptions per 100 Americans). Increasing public and regulatory attention decreased this rate by 54% from 2012 to 2017[24] to a 10-year low by 2017 (58.7 prescriptions per 100 people).[26]

As prescription opioids have become more expensive than nonmedical opioids and less available, many people with OUD have switched to nonmedical opioids. A second wave of opioid deaths, attributable primarily to heroin use, surged after 2005. Eighty percent of new heroin users reported nonmedical use of a prescription opioid in the prior year.[27] People who use heroin may switch from prescription opioids to heroin because of lower cost and ease of procurement.[28] Abundant supply and a fall in prices of nonmedical opioids have fueled a dramatic rise in OUD.[29,30] Beginning in 2013, a rise in synthetic opioids, including fentanyl and its analogs, has created a third wave of opioid deaths. These have been accompanied by a marked increase in opioid-related hospitalizations, deaths, and health care costs.[6,31–35] In many regions, nonmedical fentanyl mixed with other substances is the prevailing illicit opioid.

EPIDEMIOLOGY

Incidence of OA-OHCA

Quantifying the incidence of OA-OHCA has proved challenging. Figure 2[1,36–40] illustrates statistics on the incidence of all overdose deaths, opioid overdose deaths, and emergency medical services (EMS) treatment of opioid overdose, which approximates 50% of total EMS naloxone administration.[40] The incidence of EMS-treated opioid overdose based on naloxone administration was 104 412 cases in 2016.[40] According to historical data, 15% of these cases present in CA,[41] resulting in an estimate of 15 662 cases of EMS-treated OA-OHCA annually, or 8.9% of all EMS-treated OHCA.[9] The 2% reported incidence of OA-OHCA (0.85–1.3 cases per 100 000 person-years)[39,42] when considering US national EMS-treated OHCA incidence of 73 cases per 100 000 (180 202 adults)[9] represents ≈2500 cases per year. This is likely an underestimate because of the reasons summarized below. Fewer than 35% of opioid deaths based on medical examiner records are treated by EMS as OA-OHCA,[43] meaning that mortality reduction requires better early recognition of opioid poisoning.

Obtaining accurate data on the incidence of OA-OHCA is challenging for several reasons. First, clinical registries such as the ROC (Resuscitation Outcomes Consortium)[44] and CARES (Cardiac Arrest Registry to Enhance Survival)[45] report only whether the cause of OHCA was drug overdose without differentiating OA-OHCA from other drug-related causes of CA (eg, cocaine, alcohol).[39,42] Moreover, assignment of drug-related OHCA pathogenesis within the clinical registries is based on a positive toxicological screen during admission, evidence of empty pill bottles or drug paraphernalia at the scene, a tourniquet on the arm, or other strong corroborating evidence. Such criteria are

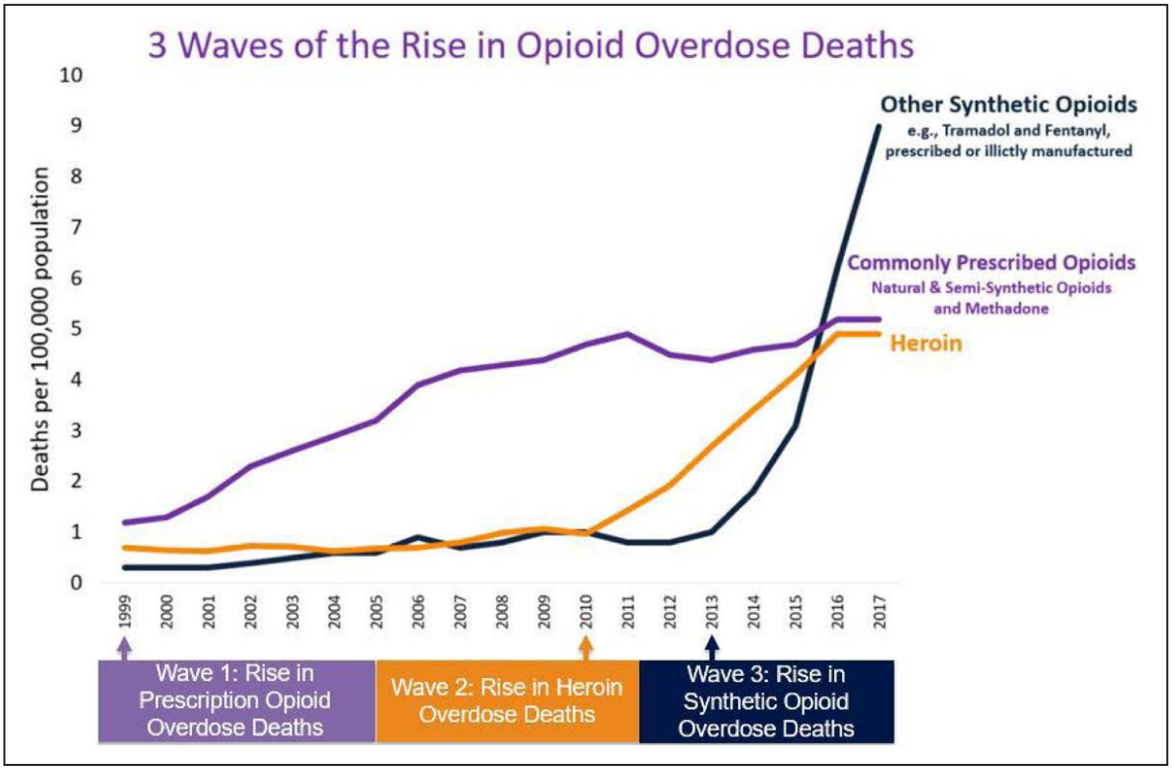


Figure 1. Historical timeline of the opioid epidemic .
Arc through time for mortality associated with opioid use in the United States. Source: National Vital Statistics Mortality File.[12]

not always met in OA-OHCA. A recent autopsy study from San Francisco County found that nearly 40% of presumed cardiac OHCAs resulted from noncardiac causes. Sixty-one percent of the above patients with a noncardiac cause (15% overall) had potentially lethal serum concentrations of opioids at autopsy,[46] implying underestimation of OA-OHCA and misclassification as a cardiac cause. Two recent reports analyzing large databases[39,42] put the incidence of overdose-related OHCA at ≈2% of all OHCAs. These data sets do not

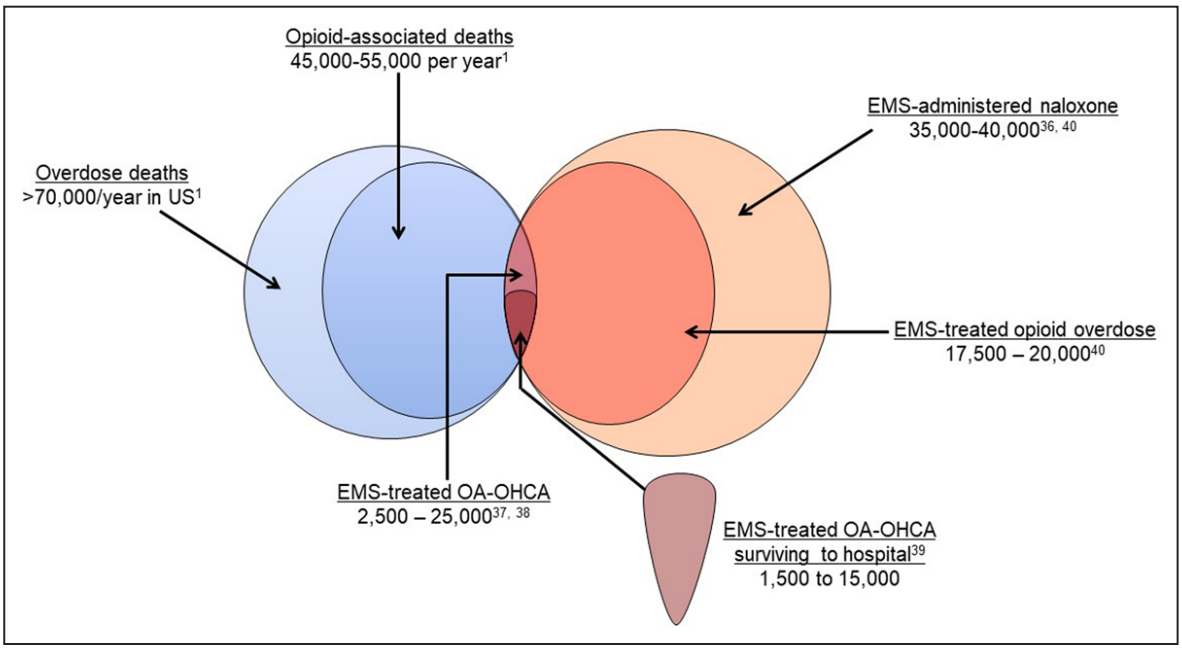


Figure 2. Incidence of opioid-associated out-of-hospital cardiac arrest (OA-OHCA) in the context of overdose deaths and naloxone use.
Venn diagram showing the distribution and overlapping prevalence of deaths from any overdose, opioid-associated deaths, and the contribution of emergency medical services (EMS)–administered treatment to the management profile of this problem.

record the cause of drug overdose, although opioid overdoses make up the majority. In contrast, contemporaneous studies that assigned cause on the basis of hospital record review suggest that the incidence is 6% to 14%[47–50] of EMS-treated OHCA or 11 000 to 25 000 OA-OHCAs annually. Computerized case definitions of sudden CA also risk misclassifying OA-OHCA.[51]

Second, most population-based estimates of OA-OHCA include only cases that received cardiopulmonary resuscitation (CPR) by EMS. Individuals with OA-OHCA discovered deceased but not receiving CPR are not included (Figure 2). No recent estimates are available for the proportion of EMS-assessed OA-OHCA left untreated, nor is it clear how often EMS is activated in the case of OA deaths. A 2004 report from King County, Washington, identified 245 patients in the year 2000 who died of drug overdose and found that 79.6% of such deaths were attended by EMS. Resuscitation was attempted in 43.5% of cases (the remainder of patients were declared dead on EMS arrival).[43] A 1993 report of individuals with presumed opioid overdoses in San Francisco (n=726) who received naloxone by EMS found that 84% had pulses on presentation, 14% had obvious signs of death and did not receive EMS treatment, and the remaining 2% in CA received CPR with a 17% rate of return of spontaneous circulation (ROSC).[41] The ratio of EMS-assessed to EMS-treated overdose-related OHCA was therefore 7:1, but this study precedes the shift to synthetic opioids and thus may not be suitable for extrapolations.

Third, national administrative data (eg, National Inpatient Sample) permit identification of OA-OHCA with *International Classification of Diseases* codes.[6] However, these data sets are limited because they do not include individuals who died in the field.[47] Lack of validation of *International Classification of Diseases* codes and variability in coding practice across hospitals also are likely to affect OA-OHCA incidence estimates.

Finally, the impact of the opioid epidemic has been uneven across the United States and the world geographically, which limits generalizing findings from regional studies.[48,49]

These limitations notwithstanding, the reported incidences of overdose-related OHCA from clinical registries and in-hospital studies are summarized in Table 1. Drug-related OHCA may be considered a proxy for OA-OHCA when the latter is not reported according to data showing that 58% to 89% of drug-related OHCA cases result from opioid use.[49,52] OA-OHCA often includes other drug classes as offending drugs: 85% of OA-OHCA cases also had a benzodiazepine or other substance present.[30,49]

- The incidence of OA-OHCA is often underestimated because of limitations in prehospital registries and shows significant geographic variation. More than half of EMS-assessed OA-OHCA cases may not be recognized as OA or may not be counted in EMS databases because resuscitation was not attempted.

Characteristics and Outcomes of OA-OHCA

Most patients with OA-OHCA are 20 to 59 years of age.[1,40,53] In contrast, OHCA with a presumed cardiac cause affects mainly patients >60 years of age (Figure 3).[42] OA-OHCA is more likely to occur at home or in a private setting and is less likely to be witnessed and receive bystander CPR, which is likely explained by circumstances associated with opioid use.[39,42,48,53] Compared with other causes of OHCA, a high proportion of patients are discovered in pulseless electric activity and asystole, whereas <10% present with ventricular fibrillation.[48,49] A summary of features associated with OA-OHCA is given in Table 2.[37,40,54–57]

Despite a higher prevalence of poor prognostic markers, survival in OA-OHCA is similar to or greater than that in OHCA with other causes. In the SHARE program (Save Hearts in Arizona Registry and Education), the survival rate was 18.6% for drug-related OHCA and 11.9% in cardiac OHCA (adjusted odds ratio [OR], 2.1).[48] These and other similar observations suggest that young age and lack of chronic comorbidities may explain similar or better survival among patients with drug-overdose OHCA.[38,42,53] Another underlying factor explaining these outcomes may be a lack of true CA in these patients. A substantial proportion of resuscitated patients with OA-OHCA arrive at the emergency department (ED) alert and neurologically normal within 5 minutes of initial assessment,[42] suggesting misclassification. That is, many of these patients may have been severely bradycardic and bradypneic, preventing EMS personnel from sensing a pulse, yet they could be rapidly and fully revived with CPR and naloxone.

PATHOPHYSIOLOGY

Physiological Effects of Opioids and Pathophysiology

Opioids exert their analgesic effects predominately through agonist binding at μ receptors in the brain and spinal cord. They also cause respiratory depression and impair sensitivity to hypoxemia/hypercarbia through mechanisms involving μ and GABA-A (γ-aminobutyric acid A) receptors and mediate euphoria through disinhibition of dopamine release.[58] The κ, δ, and ORL-1 (opioid receptor-like 1) opioid receptor subtypes also mediate these effects. Respiratory depression and euphoria are potentiated by concurrent use of GABA-A agonists, including benzodiazepines, barbiturates, certain skeletal muscle relaxants, gabapentinoids, and ethanol.[59–62]

Table 1. Incidence of OHCA

Study	Study time period	Location	Data source	Population-based	Inclusion	EMS-treated incidence*	Overall burden	Comments
Orkin et al,[42] 2017	2007–2013	Toronto, ON, Canada	RescuNet Epistry	Yes	Paramedic-treated OHCA	0.9	1.8% of all OHCAs	Unable to distinguish opioid from other causes of overdose Overdose definition assessed by paramedic using empty pill bottles, tourniquet present, other circumstantial data
Salcido et al,[39] 2016	2006–2010	7 United States 3 Canada	ROC	Yes	Paramedic-treated OHCA	1.8 (range, 0.5–2.7)	2.4% of all OHCAs (range, 0.8%–4.0%)	Unable to distinguish opioid from other causes of overdose Sufficient evidence of drug overdose included positive toxicological screen, prehospital naloxone, paramedic's note stating that the patient had overdosed
Smith et al,[48] 2018	2010–2015	Arizona	SHARE registry	Yes (80% of state population)	Paramedic-treated OHCA	2.3	5.2% of all OHCAs	Does not distinguish opioid from other causes of overdose Likelihood of drug overdose from EMS case reports, hospital charts, vital statistics data
Paredes et al,[43] 2004	2000	King County, Washington	County OHCA database	Yes	All deaths resulting from drug overdose Deaths averted by EMS response	4.3	…	Does not distinguish opioid from other causes of overdose EMS-assessed incidence reported as 8.5/100 000
Hess et al,[50] 2007	1995–2005	Olmsted County, Minnesota	EMS database	Yes	EMS-treated OHCA	0.7	10% of all OHCAs	Explicit definition of drug overdose lacking Unable to distinguish opioid from other causes of overdose
Sakhuja et al,[6] 2017	2000–2013	All US hospitals	National Inpatient Sample	No	Patients hospitalized with opioid overdose and cardiac arrest	…	≈3 million hospitalizations for opioid overdose over a 14-y period, 0.8% represented OA-OHCA	Based on *ICD* codes for opioid overdose or cardiac arrest diagnosis Potential misclassification of IHCA with OHCA Excludes patients who may have died before hospitalization
Elmer et al,[49] 2015	2009–2014	Single tertiary center; Pittsburgh, PA	Hospital-based OHCA registry	No	Patients hospitalized with OHCA and positive toxicological screen with other corroborating evidence to support drug overdose	…	14% of all hospitalized patients with OHCA met overdose criteria Opioids positive in 58% of all OA-OHCA	Drug overdose and opioid overdose based on a detailed chart review and toxicological screen Excludes patients who may have died before hospitalization

EMS indicates emergency medical services; *ICD*, *International Classification of Diseases*; IHCA, in-hospital cardiac arrest; OA, opioid-associated; OHCA, out-of-hospital cardiac arrest; ROC, Resuscitation Outcomes Consortium; and SHARE, Save Hearts in Arizona Registry and Education.

*Incidence reported per 100 000 person-years.

Opioid receptors are found in other organs, most notably the gut, lung, kidney, vascular endothelium, and cardiomyocytes.[63–67]

Some opioids, including tramadol and tapentadol, also cause serotonin agonism.[68] In overdose or in combination with other serotonergic agents, tramadol and tapentadol can cause seizures.[69,70] Methadone and LAAM (levo-α-acetylmethadol) block cardiac iKr (inward potassium rectifier, *hERG* [*human ether-a-go-go-related gene*]) channels, leading to QT interval prolongation and potentially torsades de pointes.[71] Some highly potent fentanyl derivatives cause bradyarrhythmias and asystole by depressing sinoatrial nodal recovery time.[72] Clenbuterol, a long-acting β-2 receptor

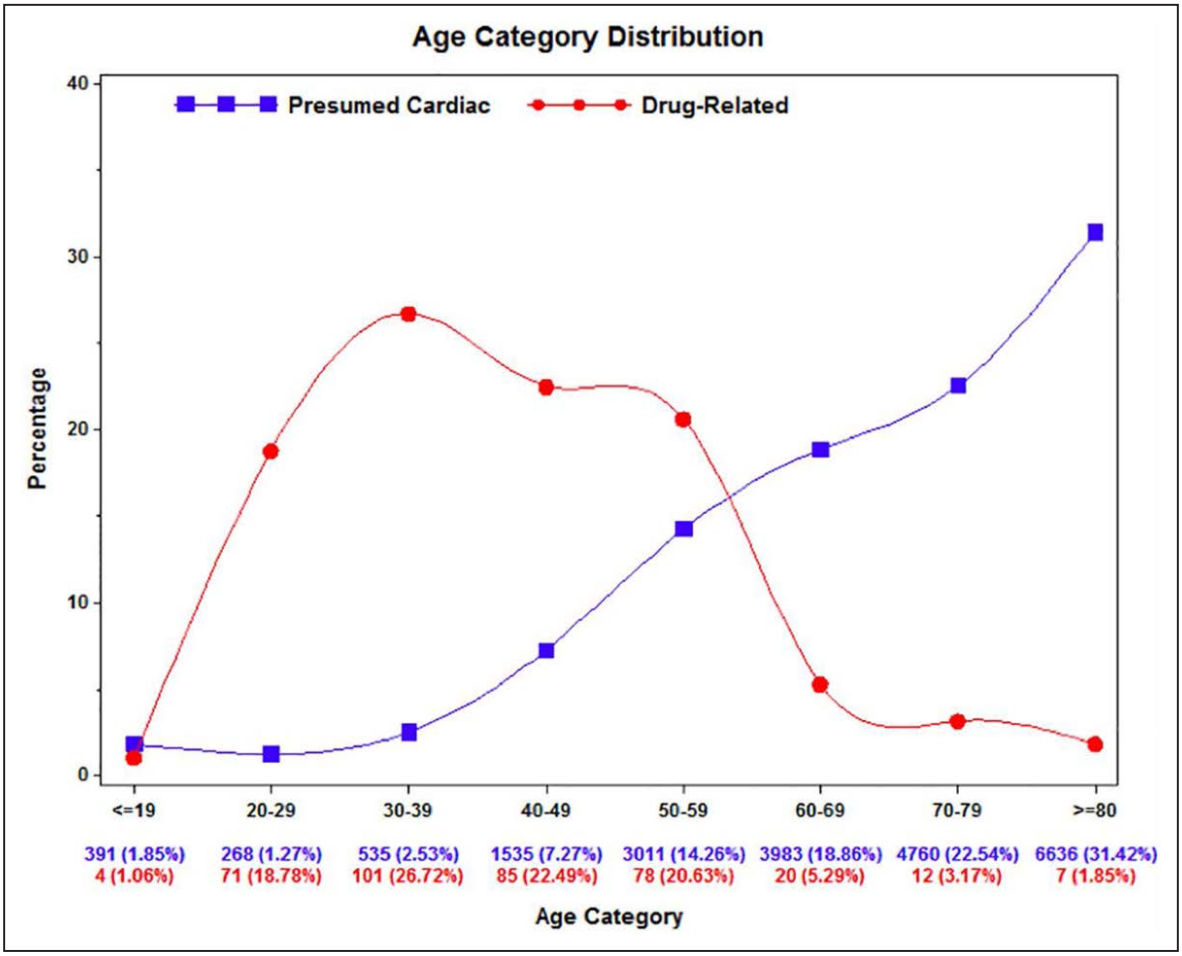


Figure 3. Proportion of overdose vs cardiac cause of out-of-hospital cardiac arrest by age.
Reprinted from Orkin et al.[42] Copyright © 2017, Orkin et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

agonist sometimes used as an additive in illicit heroin, can cause direct myocardial injury, metabolic acidosis, severe hypokalemia, dysrhythmia, and death.[73]

The relative potency of prescription and illicit opioids differs in terms of analgesia, respiratory depression, constipation, and other effects in animal models.[74] Some synthetic opioids, including fentanyl and analogues, bind μ-opioid receptors with extremely high affinity.[75] As a result, low doses can cause respiratory depression, and large doses of naloxone are sometimes required for reversal.[76] Compared with morphine and oxycodone, fentanyl and heroin result in more rapid and pronounced brain hypoxia.[77] Tolerance of the analgesic and euphoric effects of opioids develops after several days of sustained opioid use. Mechanisms of tolerance include reduction in opioid receptor availability and decreased signal transduction after receptor binding.[78] In addition, complex neuronal-glial signaling interactions and neurotransmission within brain regions affect tolerance.[79,80]

Opioid withdrawal manifests as hyperalgesia, craving, anxiety, nausea, hypertension, tachycardia, and piloerection occurring as a result of norepinephrine and epinephrine release. This may develop gradually or suddenly by the administration of an opioid antagonist (eg, naloxone) or partial agonist (eg, buprenorphine). Unlike ethanol or benzodiazepine withdrawal, the physiology of opioid withdrawal is uncomfortable but rarely life-threatening. Opioid withdrawal does require careful

Table 2. Risk Factors for OA-OHCA

History of other substance or alcohol use disorder
Comorbid medical or mental health disorders (eg, obstructive sleep apnea, depression)
High long-term dose of opioids or use of potent synthetics (eg, fentanyl)
Concurrent benzodiazepine or antidepressant use
Opioid-naïve person
Recent incarceration or inpatient hospitalization with loss of tolerance
Recent release from abstinence-based treatment program
Enrolled in opioid dependence treatment program (eg, methadone, buprenorphine, naloxone)
History of prior opioid poisoning
Social factors that result in isolation (eg, psychiatric illness)

OA-OHCA indicates opioid-associated out-of-hospital cardiac arrest.

and compassionate management because the primary risk of opioid withdrawal is high-risk opioid use and fatal opioid poisoning.[81] Buprenorphine binds to μ receptors with high affinity, displacing and preventing other opioid binding but providing only partial agonism.[82] When administered to an opioid-dependent person in withdrawal, buprenorphine reduces or eliminates withdrawal symptoms and blocks subsequent opioid efficacy. Respiratory arrest attributable to inappropriate exposure to buprenorphine in children and opioid-naïve adults has been reported, but respiratory effects are extremely rare when buprenorphine is dosed appropriately in opioid-tolerant adults.[83,84] Buprenorphine administration to an opioid-dependent person not already in withdrawal can precipitate withdrawal by replacing a full agonist (eg, heroin or fentanyl) with a partial one.[85] Selective μ agonists that provide analgesia with little respiratory depression are being developed and should increase safety.[86]

Coadministration of opioids with other sedative substances, including alcohol, whether through coprescribing, illicit polysubstance use, or both, causes synergistic respiratory depression, cardiotoxicity, and increased risk of death.[2] Autopsy studies show that most people who die of OA-OHCA have used multiple sedating substances.[87–89] Dangerous coprescription of opioids with other sedatives, particularly benzodiazepine, remains common.[59,90]

- Different opioids bind to μ-opioid receptors with vastly differing potencies and cause analgesia, euphoria, and respiratory depression to different degrees; for this reason, the risk of OA-OHCA varies between opioids. Some opioids, particularly methadone, cause dysrhythmias. Opioid antagonists reverse respiratory depression but can precipitate withdrawal; while not directly lethal, withdrawal has important negative effects. Most OA-OHCA involves concomitant use of multiple sedatives.

Brain Pathophysiology

No human clinical trials have assessed the effect of opioid agonism or antagonism on outcome from OA-OHCA. In addition to hypoxemic or hypercarbic events caused by hypoventilation, long-term opioid use can cause brain injury, particularly in the setting of injection use. Seizures have been observed more frequently in association with nonfatal fentanyl overdose and less frequently with heroin.[91] Brain pathological studies from people who use heroin[92–94] reveal evidence of recurrent infections and mycoses from presumed septic embolic disease, ischemic neuronal loss and edema likely resulting from episodes of brain hypoxia, and vasculitis.[77,95] Less common findings include leukoencephalopathy,[96] primarily after inhalation of heroin, and vasculitis or other inflammatory processes that may result from substances injected with the drug.

There is some evidence that opioids confer neuroprotection after ischemia, but the cause of ischemia in these studies is not opioid poisoning; hence, extrapolation must be done with extreme caution. A small retrospective analysis of neonates treated with analgesia after perinatal asphyxia demonstrated that opioid use was associated with improved magnetic resonance imaging findings and long-term neurological outcome.[97] Morphine preconditioning is neuroprotective against mouse global ischemia[98,99] and rat hypoxia, whereas naloxone is deleterious in a dose-dependent manner.[100] Opioid agonism is neuroprotective in rodent stroke models.[101–107] Mechanistically, morphine reduces cerebral oxygen consumption[100] and mitochondrial dysfunction after reperfusion.[108] The benefits of opioid therapy against global ischemia have been linked primarily to δ-opioid receptor activation,[109–115] although κ-opioid agonism[103,116] may also protect.

- Long-term use of opioids, particularly when injected, can cause brain injury through hypoxemia, infection, inflammation, or embolism. Opioids may be neuroprotective after brain anoxia or ischemia/reperfusion. There is a theoretical reason to suspect harm from precipitating opioid withdrawal in the ischemic brain, but no human data demonstrate this effect.

Cardiac Pathophysiology

Many opioids weakly inhibit the *hERG* channel. This is clinically significant for methadone.[117] Risk of fatal arrhythmia from methadone, which has been estimated at 14 deaths per 100 000 person-years on therapy, increases in a dose-dependent fashion and with coadministration of other prescription or illicit drugs.[80,118–122] Risk factors for methadone-induced ventricular arrhythmia include therapeutic initiation[123] or dose adjustment,[124] CYP (cytochrome P-450) 2B6 slow metabolizer status (6% of White people),[118] drugs that inhibit CYP3A4 metabolism,[117] and concomitant use of benzodiazepines[121,122,125] or antipsychotics.[121] Nonetheless, deaths from methadone overdose are more likely to result from respiratory depression, particularly when misused,[120,126] with little evidence of long-term cardiotoxicity.[127] Although most patients with OA-OHCA have structurally and electrophysiologically normal hearts, opioid use superimposed on existing cardiac disease, including the long-term cardiac effects of opioid and other drug use, may increase the risk of adverse cardiac events, including OHCA.[128,129] The cardiotoxic effects of common adulterants in synthetic opioids, including cocaine and amphetamines,[2] are well known.[130,131]

The rate of infectious endocarditis, caused by bacteria transmitted through shared or nonsterilized needles,

has increased in concert with the ongoing opioid epidemic.[132] The incidence of endocarditis from injection drug use increased from 0.48 to 0.79 per 100 000 person-years between 2003 and 2015, particularly involving the tricuspid valve.[133] Stroke rates attributable to endocarditis, which increased gradually over 2 decades (2%/y from 1993–2008), increased dramatically thereafter (20%/y between 2008 and 2015).[134]

Similar to reports in brain ischemia, δ-opioid receptor activation shows protection in experimental cardiac ischemia models when administered before or after CA or focal myocardial ischemia.[135–139] Reduction in myocardial oxygen consumption during ventricular fibrillation has been proposed as one mechanism of cardioprotection that was reversed with naloxone.[140] In the setting of cardiovascular surgery, morphine may provide additional protection compared with fentanyl.[141]

- Methadone can prolong the QT and predispose to sudden cardiac death. Endocarditis rates are increasing in pace with the opioid epidemic. δ-Opioid receptor agonism protects the heart against ischemic damage in animal models. Some causes of OA-OHCA are not reversible with opioid antagonists and require other therapy.

Pulmonary Vascular Pathophysiology

Data from cross-sectional and mechanistic studies show that opioid use can cause or exacerbate pulmonary arterial hypertension. For example, heroin use was observed in 12% and 25% of patients with pulmonary hypertension resulting from hepatic disease and HIV, respectively.[142] Morphine administration causes a vasculopathy similar to pulmonary hypertension in macaques infected with simian immunodeficiency virus,[143,144] and κ-opioid receptor agonism inhibits VEGF-R2 (vascular endothelial growth factor receptor-2)–dependent endothelial migration.[145] Pulmonary talc granulomatosis from injection drug use resulting in pulmonary hypertension and pulmonary infarction, although rare, is well described.[146,147] Septic pulmonary emboli are a common complication of tricuspid valve infective endocarditis. These effects on pulmonary circulation may increase the risk of right-sided heart failure after OA-OHCA, although clinical data are lacking.

- Long-term opioid use can cause or exacerbate pulmonary hypertension by direct and indirect mechanisms.

Pathophysiology in Other Organs

Opioids can cause aspiration of gastric contents in both therapeutic and overdose settings,[148–150] and this finding is common in autopsy series.[151] Noncardiogenic pulmonary edema is associated with both heroin overdose[152,153] and naloxone administration, with an incidence of 1.1%.[154,155] The former may be more frequent with inhalation of opioids (eg, heroin) and may vary with adulterants inhaled. The latter may result from laryngospasm and negative pressure after pharmacological reversal[155,156] and is more frequent when doses exceeding 0.4 mg naloxone are used.[154] Rapid reversal of opioid intoxication is associated with more frequent aspiration pneumonia.[157] Development of other life-threatening complications such as rhabdomyolysis with renal failure is described.[150,158,159] Because of the nature of these reports, we are unable to estimate how often aspiration, acute respiratory distress syndrome, and rhabdomyolysis complicate OA-OHCA. We summarize the organ injuries found after OA-OHCA in Figure 4[160] and highlight those not commonly noted in other forms of OHCA.

- OA-OHCA may be complicated by aspiration of gastric contents, noncardiogenic pulmonary edema, and rhabdomyolysis. Rapid opioid reversal can precipitate pulmonary edema and gastric aspiration.

Hypoxia-Ischemia Versus Ischemia

The pathophysiology of CA from opioid overdose is distinct from that of most cases of sudden, presumed cardiac OHCA. Although most opioid-related deaths involve polysubstance toxicology, in opioid overdose, progressive hypoxia is generally thought to precede the cessation of cardiac output, which manifests as pulseless electric activity or asystole.[47] The most common exception, torsades de pointes from methadone, is far less common than hypoxemic/hypercarbic arrest.[71,120] The result is a period of anoxic perfusion during which cerebral tissue oxygen content is below the ischemic threshold yet blood flow and glucose supply persist.[161] This promotes collapse of cerebral electric activity, whereas glucose delivery increases because of reflexive cerebral vasodilation increasing flow.[161,162] Hypoxic perfusion at slightly higher oxygen saturations still slows electric activity and can cause injury if prolonged[163] but is less lethal to neurons without subsequent global ischemia (CA). This is in contrast to CA caused by ventricular arrhythmias in which cardiac output and cerebral perfusion losses precede and lead to brain hypoxia.[164] Classic articles demonstrated that hypoxia with persistent glucose supply increases brain lactate by ≈2.5-fold[165] compared with similar durations of pure hypoxia[165] or ischemia.[166] Hyperglycemia during anoxic perfusion worsens acidosis and recovery of cerebral energy during reperfusion.[167–169] In experimental asphyxia, cerebral pH decreases to 6.0[170,171] compared with 6.4 in models of sudden pure ischemia.[171,172] Both cardiac injury and cerebral injury are worse after severe acidosis.[173–177] This may contribute to the observation that cerebral edema and brain death are more common after OA-OHCA

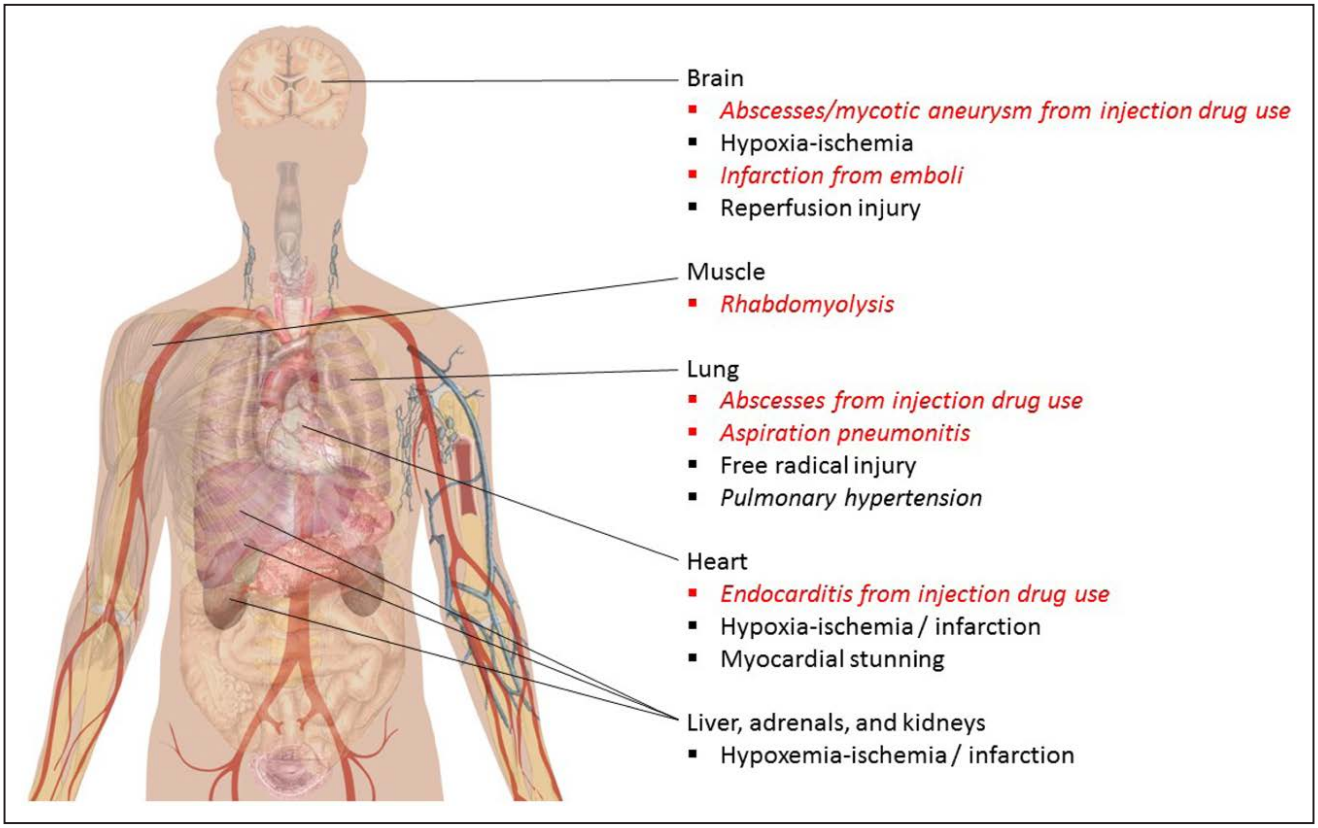


Figure 4. Organ injuries from opioid-associated (OA) out-of-hospital cardiac arrest (OHCA).
Organ injuries after OA-OHCA are often unique (highlighted in red italics) and not observed in most other forms of OHCA. Reproduced from Wikipedia Commons.[160]

than other forms of OHCA.[47,178] Reperfusion injury after hypoxia-ischemia (asphyxia) is more severe than after primary ischemia (sudden CA) in several animal models in which ischemic time was matched.[8,179,180] Mechanistically, this may result from increased reperfusion reactive oxygen species production in the brain and heart after hypoxia-ischemia versus pure ischemia.[181–194]

- Fundamental differences exist between anoxic perfusion in OA-OHCA and sudden ischemia produced by cardiac causes of OHCA. Anoxic perfusion causes more severe brain injury during ischemia and reperfusion.

PREHOSPITAL MANAGEMENT

Resuscitation of OA-OHCA often involves effort from both layperson and EMS rescuers working together to achieve ROSC and optimize patient survival (Figure 5). Many elements of conventional resuscitation practice will necessarily require modification in the era of coronavirus disease 2019 (COVID-19), particularly with respect to personal protective equipment, airway management, bystander rescue breathing, bag-valve mask use, and use of high-flow oxygen. These considerations are emerging rapidly and have been addressed by the International Liaison Committee on Resuscitation[196] and the American Heart Association.[197]

Defining Roles in Prehospital Care

In cases when OA-OHCA is likely, perhaps from available history, presence of drug paraphernalia, or individual characteristics or location, the rescuer's response will vary according to their training and the resources at their disposal. We divide prehospital responders into 3 roles (Tables 3 and 4): general public (lay bystander), trained laypeople, and health care professionals.

1. General public refers to individuals without any dedicated medical training who respond to an emergency near them. Their knowledge and actions may be based on passive public education, public service announcements, self-training such as online instruction, or stand-alone naloxone kits or provided through just-in-time instruction from 9-1-1 dispatchers.
2. Health care professionals represent the other extreme. These are trained medical providers with predefined scope of practice and resuscitation capabilities, including but not limited to nurses, nurse practitioners, paramedics and emergency medical technicians, physicians, and physician assistants. They often have formal certifications with periodic recertification and receive training that incorporates simulation and practice with resuscitation equipment. They also provide care in close proximity to additional personnel, support,

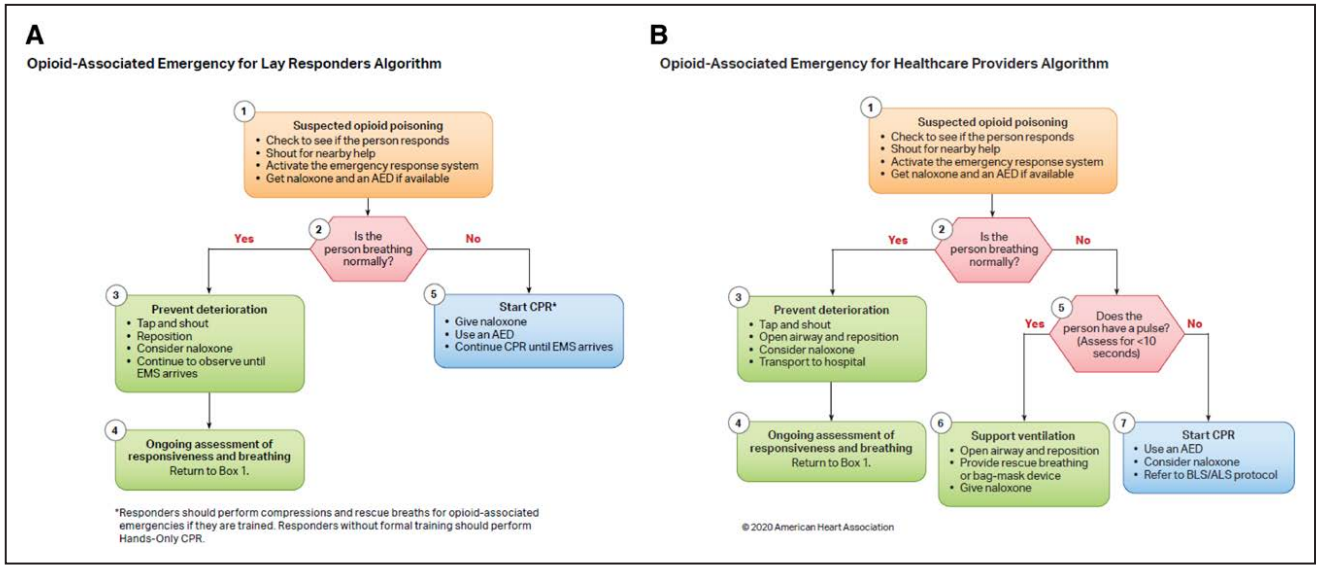


Figure 5. Suggested response to opioid poisoning.
Suggested response for (**A**) untrained and (**B**) trained responders who witness an opioid poisoning. These algorithms reflect the spectrum of poisoning, which ranges from poor response to respiratory arrest (cessation of breathing) to cardiac arrest. They incorporate the fact that responders have different levels of training and should therefore respond according to their qualification. For adults and adolescents, responders should perform compressions and rescue breaths for opioid-associated emergencies if they are trained and perform hands-only cardiopulmonary resuscitation (CPR) if not trained to perform rescue breaths. For infants and prepubertal children, CPR should include compressions with rescue breaths. Whether naloxone is needed to prevent respiratory arrest in an unresponsive but normally breathing individual is variable. Although naloxone has no proven role in treating cardiac arrest, some proportion of respiratory arrests are likely misclassified as cardiac arrest. In these cases, naloxone administration early in the resuscitation may result in a rapid resumption of breathing and improvement in circulation, although dose titration may be needed to fully antagonize more potent synthetic opioids such as fentanyl. AED indicates automated external defibrillator; ALS, advanced life support; BLS, basic life support, and EMS, emergency medical services. *Responders should perform compressions and rescue breaths for opioid-associated emergencies if they are trained. Responders without formal training should perform hands-only CPR. Adapted from Panchal et al.[195] Copyright © 2020, American Heart Association, Inc.

and resuscitative equipment. For OA-OHCA, this group may also include personnel working in dedicated overdose prevention and supervised consumption settings.

3. Trained laypeople represent an intermediate group in terms of training. Their abilities may span a broad spectrum. Concise training in the form of overdose education and naloxone distribution (OEND) programs teaches participants to respond to a patient with opioid poisoning using naloxone and may be lifesaving.[198–200] In areas where the opioid epidemic is prevalent, volunteer harm reduction workers and first responders (eg, police, fire, librarians) operate as paraprofessionals with training and resources that may approximate those of EMS, including the ability to deliver high-quality CPR, rescue breathing, and naloxone.[201] OEND is associated with reduced opioid-related and all-cause deaths,[202–206] and the absence of such training is associated with higher mortality.[207] In some jurisdictions, paraprofessional harm reduction and overdose prevention personnel have emerged with extensive experience in responding to and reversing overdose. These are not laypeople in the conventional sense because they perform resuscitative interventions routinely, often working in settings with medical equipment (oxygen, basic airway management tools, vital sign monitors, etc), and thus approximate health care providers.

As described in the 2015 American Heart Association guidelines update (Supplemental Figure 1), optimizing outcomes after OA-OHCA requires responders to identify opioid-related poisoning as a health emergency and get appropriate help, provide interventions to prevent the deterioration of respiratory depression to CA, and provide interventions to improve survival from OA-OHCA. Appropriate and targeted educational approaches or public messaging can permit the general public, trained laypeople, and health care professionals at all levels of training to contribute to these 3 essential goals. We provide suggested responses based on level of training and the extent of opioid poisoning (Figure 5). These differ from standard approaches to OHCA in the consideration of naloxone use and CPR, including rescue breathing, by trained rescuers. Emergency telecommunicators (aka dispatchers) play an important role in instructing members of the public to recognize CA and provide lifesaving interventions before the arrival of EMS.[208] In many cases of OA-OHCA (83.3% in 1 study),[209] telecommunicators lack sufficient information to recognize that opioids are involved in the emergency. By default, the response in these cases will follow standard EMS procedure until the opioid emergency is recognized.

- Prehospital response to OA-OHCA is shaped by the training of the rescuer(s), which defines their roles

Table 3. Definitions of Individuals Responding to OA-OHCA Based on Training

	Definition	Likely educational settings/ resources
General public	Untrained lay public	Public service announcements Stand-alone OEND kits Virtual/online courses EMS dispatcher instructions
Trained laypeople	Non-health care personnel with formal training Naloxone dosing Basic life support Other skills	OEND programs Occupational first-aid programs Instructional (certification) courses for people likely to encounter overdose
Health care providers	Existing health care professionals with resuscitation capabilities	Formal health care training Resuscitation training Ongoing quality improvement and simulation

EMS indicates emergency medical services; OA-OHCA, opioid-associated out-of-hospital cardiac arrest; and OEND, overdose education and naloxone distribution.

(Tables 3 and 4) and ability to intervene (Figure 5). Optimizing outcomes after OA-OHCA requires appropriate training for those individuals likely to encounter individuals with opioid poisoning.

Recognition and Activating Emergency Response

OA-OHCA can occur rapidly and may be misinterpreted as common behavior associated with opioid intoxication such as snoring or falling asleep.[210]

Table 4. Roles of Individuals Responding to OA-OHCA Based on Training

	General public*	Trained laypeople*	Health care providers*
Recognizing opioid poisoning	+/–	+	+
Using stimulus to assess individual's response	+	+	+
Differentiating cardiac from respiratory arrest	–	+/–	+
Using vitals and cardiac monitors	–	+/–	+
Identifying opioid poisoning vs other drug poisonings	–	+/–	+
Activating EMS	+	+	+
Administering naloxone	–	+	+
Titrating naloxone dose	–	–	+
Performing chest compressions	+	+	+
Performing rescue breathing with a mask or face shield	–	+/–	+
Using bag-valve mask and oxygen	-	+/–	+
Using automated defibrillator	+/-	+	+

EMS indicates emergency medical services; and OA-OHCA, opioid-associated out-of-hospital cardiac arrest.

*For definitions of these groups of individuals, see Table 3.

Early identification of opioid poisoning is critical to avoid deterioration to OA-OHCA because survival is very likely when EMS assesses the individual before OHCA.[41,43] Early first-aid interventions, including ventilations or administration of naloxone, provide definitive treatment. When a person does not exhibit obvious signs of life or respond purposefully to painful stimuli, it may not be possible to rule out CA through pulse checks.[7,211] Severe opioid-mediated respiratory depression may appear similar to agonal breathing and OA-OHCA. EMS should be called when OA-OHCA is suspected or patients fail to respond to basic interventions by trained laypeople. EMS may institute advanced interventions, including escalating doses of naloxone and advanced airway management,[209] which may prevent OA-OHCA if not already present. The general public and trained laypeople are familiar with and able to call 9-1-1, but barriers to calling, including fear of arrest, are well documented.[212–215] Good Samaritan legislation enhances responders' willingness to call 9-1-1 and remain with the patient until emergency personnel arrive,[216,217] but misunderstanding of this legal protection is common among responders[217,218] and law enforcement officers.[219]

- First responders should presume OA-OHCA when individuals with suspected opioid poisoning do not respond to basic interventions and activate EMS while performing CPR.

Rescue Breathing and Airway Management

Most opioid overdoses deteriorate to OA-OHCA as a result of loss of airway patency and lack of breathing; therefore, even when opioid reversal with naloxone is possible, respiratory failure must be addressed to stabilize the individual. Data on the best approach to airway management are lacking, and level of training influences the outcomes to different airway management approaches. OEND participants are willing to perform rescue breaths, and many report doing so when they respond to opioid overdose.[206] It is not clear whether rescue breathing is more effective than opioid antagonism to enhance respiratory drive in opioid-mediated respiratory arrest, and the 2 approaches are perhaps additive. If multiple lay responders are available, 1 responder may perform a jaw thrust maneuver, which reduces airway obstruction and provides harmless painful stimuli that may promote spontaneous breathing.[220] The airway can also be opened by performing a head tilt–chin lift.[7,221–223] This may be followed by delivery of a rescue breath through mouth-to-mouth breathing, a protective mask, or bag-valve mask with oxygen while ensuring sufficient tidal volume for good chest rise.[221,223] CPR education research demonstrates

that effective rescue breathing is among the most difficult skills for laypeople to acquire, perform effectively, and retain and that the skill cannot be acquired with minimum proficiency without dedicated learning time and hands-on practice.[224–226] Performing ineffective rescue breathing or other airway maneuvers may detract from other essential interventions and ultimately reduce the effectiveness of the overall resuscitation. Therefore, airway and rescue breathing interventions should be recommended for those with sufficient training. Rescue breathing training with hands-on practice should be incorporated into general public education whenever possible. General public responders who are not trained to provide rescue breathing or airway management should provide all other resuscitative interventions, including activating EMS, administering naloxone, and performing chest compressions. EMS teams may consider the use of advanced airway approaches such as supraglottic airway placement or endotracheal intubation,[227] although no studies have directly evaluated the efficacy of these approaches in OA-OHCA. In a 5-year retrospective review of endotracheal intubation on patients with drug overdose, the use of intubation was rare (3.5%) but with few complications.[228] Those at greatest risk of requiring intubation had underlying obstructive lung disease or coingestions. Three recent randomized controlled trials have attempted to address the use of airway management during OHCA.[229–231] In summary, these studies suggest that the use of endotracheal intubation when intubation success rates are high produces outcomes similar to the use of supraglottic airway.

- OA-OHCA requires attention to airway management and breathing, which are difficult skills to learn and retain. EMS professionals should select an airway device for OA-OHCA on a case-by-case basis, taking into consideration local standards, clinical context, and the provider training.

Compression-Only Versus Conventional CPR

Rapid activation of EMS concurrently with CPR is critical because individuals with OA-OHCA will require professional medical intervention.[221] Chest compression–only CPR became the standard approach for layperson bystander CPR in 2010 in an effort to simplify and focus rescue efforts on high-quality chest compressions[232] and according to data showing no survival benefit when ventilation was added to bystander resuscitation.[233] However, the preclinical literature in support of compression-only CPR focuses primarily on models of ventricular fibrillation that simulate OHCA with a cardiac cause[234,235] when the individual is fully oxygenated at the time of arrest,[164,236] in contrast to most OA-OHCAs.[161] In randomized clinical trials, asphyxial CAs were excluded from enrollment.[233,237,238] When adult patients with a noncardiac cause or nonshockable OHCA have been considered in subgroup analyses, conventional CPR is associated with improved outcome over compression-only CPR in some studies but not in others.[239,240] The recommendation for individuals with appropriate training to perform compression-ventilation CPR in cases of asphyxia CA such as OA-OHCA is based on physiological rationale. Ideally, when EMS teams perform resuscitation, compression-ventilation CPR can be provided with uninterrupted chest compressions.

- Rescue breaths in addition to high-quality chest compressions (conventional CPR) are likely preferable in resuscitation of individuals with OA-OHCA. Conventional CPR requires adequate training and willingness on the part of the trained layperson.

Opioid Antagonism Before and After OA-OHCA

Naloxone binds μ_1-opioid receptor with high affinity, displacing opioids. It is administered most commonly by intramuscular, subcutaneous, intravenous, or intranasal routes, although intraosseous infusion may also be appropriate.[241–244] Successful administration of naloxone by nebulization in spontaneously breathing patients has been reported.[245] Although naloxone can be administered by instillation into an endotracheal tube, it is difficult to envision a situation in which this route of administration would be preferred. For intoxicated non–opioid-dependent individuals (eg, a child who ingests a parent's opioid medication), naloxone restores consciousness and breathing without adverse effects. In opioid-dependent individuals, however, naloxone can precipitate withdrawal in a dose-dependent fashion.[81] The effective duration of naloxone is 30 to 90 minutes.[246,247]

Naloxone administration may reverse respiratory depression and prevent OA-OHCA. The presence of miotic pupils in a prehospital patient with altered mentation is strongly associated with naloxone responsiveness (OR, 20).[248] Because precipitated withdrawal is uncomfortable for patients and may erode therapeutic alliances between clinicians and people who use drugs,[81] the lowest effective dose of naloxone that restores adequate respirations and protective airway reflexes should be used. This also minimizes adverse effects such as agitation and pulmonary edema.[154] In the era of potent synthetic opioids such as fentanyl, predicting the optimal dose may be challenging, with higher doses necessitated in some cases.[249,250] Whereas providing assisted ventilation, starting with a low dose of naloxone, and titrating repeat naloxone doses to restoration of protective airway reflexes and adequate spontaneous respirations is the ideal treatment in the EMS or ED setting, this approach is not practical for lay rescuers. For this

reason, presentations of naloxone intended for intramuscular or intranasal administration by the lay public incorporate a 2-mg dose, which is more than the initial recommended intravenous dose for health care professionals.[7,251] In the prehospital setting, the need to rapidly reverse hypoventilation may take priority over avoiding precipitated withdrawal. The ideal initial dose of naloxone in the OA-OHCA setting when there is a high likelihood of potent synthetic opioid involvement is unknown. Preventing OA-OHCA and restoring spontaneous breathing is always the prevailing goal. In individuals with a pulse, airway and ventilation support should be provided according to the responder's level of training while naloxone is being obtained until effective spontaneous respiration is restored. If there is any doubt about circulation, chest compressions should be provided first. A reversal agent of opioid-induced respiratory depression that avoids analgesia loss is being investigated.[252] Although use of buprenorphine in lieu of naloxone to treat OA respiratory arrest without provoking severe withdrawal has been described, the practice has not been systematically tested.[253]

The effect of naloxone use during CPR on OA-OHCA outcomes is uncertain. Clearly, some patients present with respiratory arrest and faint or difficult-to-palpate pulses; these patients are likely to benefit from naloxone. One study reported improvement in cardiac rhythm when naloxone was administered along with other resuscitative measures.[254] However, this study reports changes in rhythm that do not clearly associate with improved outcome, and the study lacks a control group. A rat asphyxial CA study reported similar ROSC rates when naloxone was compared with epinephrine during CPR,[255] although it is possible that this was attributable to endogenous catecholamine release triggered by naloxone. Two other studies failed to show significant improvements in ROSC or neurological outcomes when naloxone was added to epinephrine.[256,257] These studies are limited by small numbers (n=8 per group) and lack of opioid use to induce arrest.[255–257] Numerous animal studies have demonstrate neuroprotection and cardioprotection associated with opioids in the setting of CA (see the Brain Pathophysiology and Cardiac Pathophysiology sections). In most studies of experimental brain ischemia, reversal of opioid binding with antagonists such as naloxone, naltrexone, or naltrindole (δ-opioid receptor specific) worsened brain injury,[104,109–115] although some studies reported a neutral effect.[101,108] Some reports, primarily in experimental stroke, show neuroprotection resulting from naloxone,[258–260] and 1 report shows naltrexone neuroprotection after experimental CA.[261] Opioid antagonism, particularly at high initial and total doses, is associated with pulmonary edema[154] with the overall incidence of this complication reported as 1.1%. Pulmonary edema may be mediated by negative pressure when reversed patients inspire against a closed airway[156] or sympathetic overload with malignant hypertension.[155] In summary, naloxone does not have a likely benefit in patients with confirmed CA who are receiving standard resuscitation, including assisted ventilation, and there are some reasons to suspect that this practice may cause harm by increasing cerebral metabolic demand at a time of hypoxemia and acidosis.

Finally, it is clear that a majority of OA-OHCAs occur in the setting of another substance present (eg, benzodiazepine),[30,49] which potentially worsens the respiratory depression. Because it is impossible to know at the moment resuscitation is needed what classes of drugs are poisoning the individual and causing respiratory depression, health care providers should be aware of their local OA-OHCA epidemiology. In areas where benzodiazepine cointoxication is known to occur at high levels, rescuers may consider antagonizing this class of drugs as well to restore normal breathing if naloxone is unsuccessful even in higher doses. No data are available to assess the potential benefits of combination antagonism versus the risks of adverse effects from flumazenil such as convulsions or supraventricular arrhythmias.[262]

- If the patient is definitely pulseless and receiving standard resuscitation, including assisted ventilation, naloxone is unlikely to be beneficial. Because there is a theoretical basis for harm, standard resuscitation alone is indicated. Opioid antagonism to prevent OA-OHCA in patients with OA central nervous system and respiratory depression is always reasonable and should be delivered along with CPR when it is uncertain whether the patient is pulseless. Dose titration of naloxone for patients with central nervous system and respiratory depression may be required when potent synthetic opioids have been used, but overantagonism has potential adverse events.

EMS Management After Return of Consciousness With Adequate Respirations: Transport Decisions

As prehospital naloxone becomes more available, resedation and recurrent respiratory arrest are important concerns. Several studies conducted predominately in people who use heroin demonstrated apparent safety (ie, no short-term mortality) when patients were allowed to refuse ambulance transportation to the hospital.[263–268] Brief ED observation protocols also have been used successfully in patients with presumed heroin and fentanyl poisoning.[269–271] These practices apply only to respiratory arrest, not OA-OHCA. Recent EMS guidelines[272] view naloxone use as an opportunity to connect high-risk patients[273] with treatment services. In addition, EMS must consider the potential variability in naloxone response/duration with more potent synthetic

agents, long-acting opioids (eg, methadone), and the potential for polypharmacy.[2,274,275] During the observation period, patients who are not obviously awake and conversant should have continuous end-tidal CO_2 and pulse oximetry monitoring. One small trial has examined a possible role for single-dose oral naltrexone after long-acting opioid (methadone) overdose, but further work is necessary.[276]

- Although most data support safety when individuals reversed from severe respiratory depression caused by opioid poisoning refuse EMS transport, this should be viewed with caution given increasingly common polypharmacy and long-acting opioids. Individuals with OA-OHCA requiring CPR should be transported to the hospital.

POSTRESUSCITATION CARE

Patients resuscitated from CA are at high risk of rearrest, multisystem organ failure, neurological disability, and death.[277] From 2009 to 2015, there was a 34% increase in overdose admissions requiring intensive care unit (ICU) support and an associated increase in mortality in these patients from 7% to 10%.[32] Major goals in postresuscitation care are the exclusion of causes of arrest that require emergent treatment, prevention of secondary brain injury, and best-practice critical care. Accurate neurological prognostication is important to avoid premature withdrawal of life-sustaining therapy, and postacute rehabilitation and secondary prevention are imperative for survivors. The distinct pathophysiological features of OA-OHCA[8] (see Pathophysiology section) suggest unique needs for this growing patient population but data are lacking.

Determining Arrest Cause

Among patients with ROSC and a secured airway, no disease-specific treatments exist for OA-OHCA compared with OHCA in general. In contrast, there are many other types of OHCA that require specific treatments (eg, myocardial infarction, stroke, others).[47,278,279] These alternative or perhaps coincident causes must be systematically considered in OA-OHCA. Because drug testing does not take into effect timing or tolerance, detection of an opioid or metabolite in body fluids should not be used to establish cause of CA in the absence of additional history.[280] In addition, some laboratory methods fail to detect synthetic opioids.

Targeted Temperature Management

Targeted temperature management (TTM) attenuates several mediators of secondary brain injury after OHCA and is the standard of care for patients who are comatose after ROSC.[277,281–283] The effect of TTM after OA-OHCA specifically is unknown. Concerns that hypothermia slows drug metabolism, prolongs the QT interval, and may promote bradyarrhythmias have led some to question the safety of TTM after toxin-induced OHCA,[284] although the connection of these known effects to harm is theoretical. The role of TTM in the management of patients with nonshockable initial arrest rhythms, which are common in OA-OHCA,[47] remains uncertain because these patients are underrepresented in clinical trials.[38,281,282,285–289] Present guidelines consider provision of TTM in these situations an option. Khan and colleagues[290] explored the association between TTM and recovery after OA-OHCA and found TTM to be associated with a 14% increase in odds of survival to hospital discharge with favorable discharge disposition (home or inpatient rehabilitation).

- Current guidelines support consideration of TTM use in patients with nonshockable initial rhythms, and there is no evidence to suggest harm in patients after OA-OHCA.

Treatment of Shock

Postresuscitation shock affects 14% to 54% of patients with OHCA with ROSC.[282,291,292] Transient myocardial dysfunction is common (66%–77%) and is classically followed by delayed systemic vasodilation, which may result from sterile inflammation, infection, or a critical illness–related corticosteroid insufficiency.[291–297] Hemodynamic profiles after OA-OHCA are not well described. Indirect evidence suggests that contributors may include (1) rebound opioid toxicity after naloxone metabolism, which may contribute to sympatholysis, although not sympathetic receptor blockade; (2) concurrent toxidromes caused by coingestions; (3) hypothermia resulting from intoxication or environmental exposure; (4) hypovolemia caused by poor prearrest oral intake; and (6) prearrest sepsis and aspiration, which can worsen systemic inflammation.[43,220,274,298–300] During initial assessment, it is reasonable to administer intravenous crystalloids in hypovolemic patients, although the use of routine prehospital crystalloids to induce hypothermia is contraindicated.[301] Norepinephrine is a reasonable first-line vasopressor in undifferentiated shock.[302,303] A causal relationship between higher blood pressure and survival remains uncertain.[294,304,305]

- Clinicians treating patients with OA-OHCA with shock should use a systematic approach to identify causes of shock. Reasonable initial resuscitation may include crystalloid to correct hypovolemia and norepinephrine to correct hypotension.

Ventilator Management

Although the majority of opioid overdose patients who have respiratory depression without CA are successfully

managed without intubation,[57] some patients will require intubation and mechanical ventilations, as will all patients with OA-OHCA who do not awaken after ROSC. Aspiration pneumonia and acute respiratory distress syndrome are common after OA-OHCA.[306] Management of pneumonia with appropriate antibiotics[307] and acute respiratory distress syndrome with lung protective strategies[308] are reasonable as recommended in recent guidelines. Optimal oxygen and carbon dioxide goals remain an area of active research and have been considered in the postresuscitation care guidelines.[277] Current evidence supports maintaining oxygen saturations >94% to avoid hypoxia and hyperoxia and normal carbon dioxide targets ($Paco_2$ = 35–45 mm Hg). Whether mild hypercarbia is neuroprotective is the subject of ongoing clinical trials[309,310] because a pilot human study[311] and observational data[312] suggest potential benefit.

Sedation and Shivering

As with all CA survivors, indications for sedation and analgesia after OA-OHCA include treatment of pain, anxiety, ventilator dyssynchrony, shivering during TTM, control of agitated delirium, treatment of seizures or myoclonus, or management of opioid withdrawal.[277,294,304,313] A small randomized trial suggested that sedation with medications with a short half-life may facilitate earlier extubation and neuroprognostication.[314] Common medications used during TTM are presented in Supplemental Table 1. In general ICU populations, use of validated sedation assessment tools minimizes oversedation, shortens the duration of mechanical ventilation and ICU length of stay, and reduces the need for tracheotomy.[315,316] Routine use of validated pain scales has also been associated with improved outcomes.[316,317] Patients with OA-OHCA often have significant tolerance and may withdraw if not provided opioids as part of their sedation regimen, although this has not been examined. Opioid withdrawal in the post-ROSC course could complicate management and prognostication. Shivering can also be controlled nonpharmacologically with magnesium or skin counterwarming.[318]

- ICUs that care for OA-OHCA should use validated sedation and pain assessment to titrate therapy to individual needs.

Neuroprognostication After OA-OHCA

Referent gold standard tests for neuroprognostication do not exist, and critical care treatments such as TTM and sedation can interfere with diagnostic modalities.[319,320] Prognosis and limitation of life-sustaining therapies after OA-OHCA often differ from practice after other forms of OHCA because of the patients' young age and fewer comorbidities,[321] as well as delayed opioid, coingestant, or sedation metabolism in the setting of postarrest shock, TTM, and liver/kidney dysfunction.[322]

Many patients who are initially comatose after OHCA will awaken ≈3 days after admission.[323,324] A sizable subgroup regains consciousness >72 hours after ROSC.[325,326] These patients have a greater incidence of circulatory shock after ROSC and impairments in renal function.[325] Guidelines recommend delaying neurological prognostication until at least 72 hours after ROSC or normothermia.[277,323,327] Unfortunately, postarrest patients are often subjected to early withdrawal of life-sustaining therapy despite these guidelines.[324,328] It is not known whether awakening after OA-OHCA differs from awakening after other forms of OHCA and whether these patients require alternative neuroprognostic approaches. Caution is warranted when evaluating for death by neurological criteria (brain death) in the setting of potential intoxication,[329] particularly in the setting of severe poisonings or if long-acting medications were used. Because most patients with OA-OHCA have used multiple sedating substances, drug metabolism is slowed during TTM, and the elimination of some drugs is prolonged during overdose, relying on the reference pharmacokinetics of a suspected culprit opioid is not a way to reliably exclude continued drug toxicity as a cause for sedation.

- Given the potential for delayed clearance of intoxicants after OA-OHCA, a stepwise approach to prognostication in most cases should delay decisions about withdrawal of life-sustaining therapy until (1) at least 72 hours after ROSC and normothermia, (2) initial intoxicants and their metabolites have cleared, and (3) ICU-administered sedatives and analgesics have cleared.

Surveillance for Adverse Cardiovascular Events

Patients with life-threatening drug overdose (but excluding those with OA-OHCA) who require hospitalization are at risk of developing cardiovascular events such as myocardial injury, persistent shock, dysrhythmia, or CA during hospitalization.[330] Independent risk factors for cardiovascular events in adult patients with overdose include QT prolongation (multivariate OR, 27.6), metabolic acidosis (OR, 4.4), and prior cardiac disease (OR, 9.5).[128] An ECG at the time of admission is therefore indicated for admitted patients with overdose.[331] Lactic acidosis (serum lactate ≥5.0 mmol/L)[332] and elevated serum troponin I on admission (OR, 21.1)[333] are particularly strong risk factors for death in adult patients hospitalized for drug overdose. Among pediatric patients, long QT (OR, 2.8) and metabolic acidosis (OR, 2.3) were risk factors, and adolescents were at greater risks than children 0 to 12 years of age.[334]

Prevention of ICU Complications

Critically ill patients, including those resuscitated from OA-OHCA, are at risk for complications such as ventilator-associated pneumonia (10%–20%), catheter-associated bloodstream infection (4.4–7.6/1000 days), delirium (24%–41%), malnutrition (12%–56%), and venous thromboembolism (2%–4%).[298–300,303,335–340] Aspiration pneumonitis is more common in comatose patients found in the supine or lateral decubitus position[341] (most OA-OHCA). OUD has been associated with a rise in endocarditis,[132,342] hepatitis C, HIV,[132] and other skin and soft tissue infections.[343] Numerous trials demonstrate that ICU complications can be prevented through adoption of guideline-recommended preventive protocols and standardized care bundles.

- We endorse existing critical care societal guidelines intended to reduce complications such as ventilator-associated pneumonia, central line infection, delirium, enteral nutrition, and venous thrombosis in the management of patients with OA-OHCA.[303,316,335,337,344–346] Patients with OUD are more likely to have certain infections.

Secondary Prevention and Rehabilitation

Patients who survive admission for opioid poisoning are at high risk of having another overdose event and death.[55,273,347] Secondary prevention measures may reduce risk of death among people who use opioids regularly[201,348] and should be considered before discharge in OA-OHCA survivors with good neurological function.

Brief Counseling

Structured approaches to counseling such as Screening, Brief Intervention, and Referral to Treatment and the Brief Negotiation Interview have been shown to have a modest reduction in ongoing OUD.[349] The effectiveness of these interventions shortly after resuscitation from life-threatening opioid overdose and for patients in severe opioid withdrawal, however, is not known.

Medications for OUD

Medications for OUD (MOUD), typically involving methadone or buprenorphine, are more effective at treating OUD than counseling alone.[350] Among patients in the ED, adapting the Screening, Brief Intervention, and Referral to Treatment approach to include counseling, immediate initiation of buprenorphine therapy, and referral to ongoing MOUD care results in improved retention in treatment compared with use of the Brief Negotiated Interview plus referral from the ED to a specialized treatment center.[351] A growing number of EDs offer initiation of buprenorphine treatment and referral to ongoing care on demand.[351–353] Whether similar results could be obtained among hospitalized patients who recover from OA-OHCA is unknown. It is uncertain whether initiation of MOUD is beneficial after the prolonged in-hospital course that generally follows OA-OHCA during which tolerance and withdrawal have resolved. One-year opioid-related mortality was still 1.4% with the use of MOUD,[350] yet risk of overdose after loss of tolerance also occurs.[354]

Take-Home Naloxone

Many EDs prescribe or dispense naloxone to patients at high risk of opioid overdose, including overdose survivors.[202,206,355] This practice reduces subsequent mortality among recipients and in the community.[202,356] One ED program demonstrated a two-thirds acceptance rate in patients using opioids to take-home naloxone (THN).[253,357]

Basic Life Support Education

No data exist on providing basic life support education to families of patients with OA-OHCA. This would be reasonable because OUD has clear familial and genetic links[358–360] and is more common in specific neighborhoods.[361] OA-OHCA is more common when a family member is prescribed an opioid, particularly in children and adolescents and at higher prescribed doses.[362]

Inpatient or Outpatient Therapy

Discharge of OA-OHCA survivors into drug treatment programs, both inpatient and outpatient, should be considered because both have demonstrated efficacy in reducing relapse with slightly reduced relapse rates after inpatient treatment.[363,364] Prolonged inpatient admission with loss of tolerance may be associated with subsequent opioid-related death.[354] In the context of both inpatient treatment and outpatient groups (eg, Narcotics Anonymous), spiritual renewal, spirituality, and specific religious practice/attendance have been associated with reduced relapse rates, improved self-esteem, and less depression, although they are less effective than MOUD-based therapies in maintaining abstinence.[365–368] Other important factors included friend and family relationships[365,369] and relationship with a therapist.[369] Treatments including MOUD and THN have the best evidence supporting mortality reduction.

- OUD often results in overdose and OA-OHCA.[348] Secondary prevention such as MOUD, THN, counseling, religious and spiritual services, and basic life support training to patients or family members and subsequent inpatient or outpatient therapy should be considered as part of discharge planning.

IMPLEMENTATION OF SCIENCE

US Surgeon General Dr Jerome Adams has identified lay responses to opioid overdose and engagement in OEND programs as "a key part of the public health response to the opioid epidemic."[198] Similar statements have been issued by Health Canada and the World

Table 5. Populations at Elevated Risk for Opioid Overdose and Non–Health Care Providers Likely to Benefit From OEND Programs

Populations at elevated risk of overdose and fatal overdose
People with an OUD
People with polysubstance use disorder
People who use opioid alone
People who inject opioids
People prescribed MOUD, including methadone and buprenorphine, particularly at high-risk periods such as induction or discharge
People with a history of OUD who have experienced a period of withdrawal (such as detoxification, hospitalization, or incarceration)
People receiving prescription opioids with risk factors for adverse events
Coprescriptions of benzodiazepines or other sedatives
Ongoing alcohol use or alcohol use disorder
High-dose prescription opioid therapy (>50–100 mg/d morphine equivalent)
Non–health care populations likely to witness overdose
People living with or in frequent contact with any of those listed above
Friends and family members of people who are at risk of overdose
Community center, public library, and shelter personnel
Police, fire and other nonmedical first responder personnel
Nightclub and festival personnel
Sex workers
People who sell illicit drugs

MOUD indicates medications for opioid use disorder; OUD, opioid use disorder; and OEND, overdose education and naloxone distribution.

Data derived from references [210] and [371–381].

Health Organization.[200,370] Enhancing public capacity to recognize and respond to opioid-related emergencies is a compelling imperative but introduces a range of challenges for implementation. A variety of educational modalities are required to reach the broadest audience, ranging from ultrabrief public service announcements and advertising to involved day-long or multiday training in naloxone administration, rescue breathing, and CPR for those most likely to attend to opioid-related emergencies (Table 5).[210,371–381] Like other resuscitation processes, minimizing mortality from OA-OHCA is subject to the principles of the Utstein formula (Figure 6),[382] which posits that survival rates are the product of best science, educational context, and local implementation, but is perhaps further complicated by the complex sociopolitical milieu where opioid overdose occurs.[382] These contextual elements (eg, naloxone or Good Samaritan legislation) are subject to rapid changes, have substantial impact on opioid-related mortality, and must be considered together to determine local best practices. Optimal training duration, frequency, intervals for retraining, and other variables have not been well studied. Other than studies relying on participant self-report, there is little research on the educational efficacy of overdose education programs.[383,384]

Compression-Only and Conventional CPR

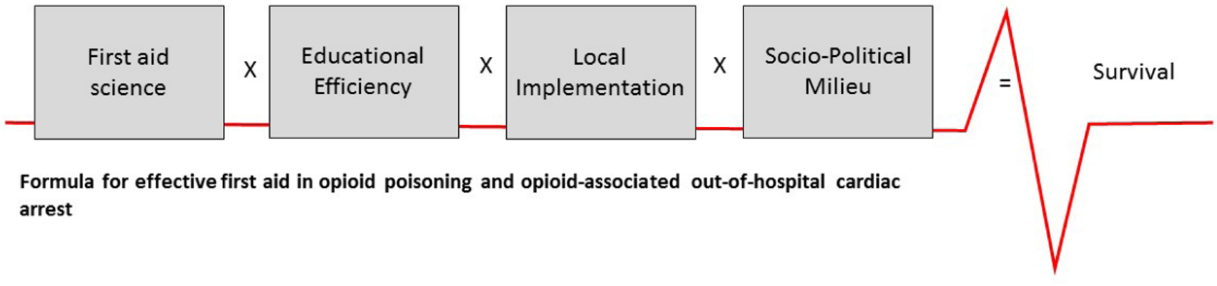
Laypeople can learn to perform chest compressions quickly and effectively and retain the skill better than other resuscitative interventions, including through ultrabrief and self-taught training interventions.[385,386] Broadly targeted education can prepare the general public to perform chest compressions for people with OA-OHCA.[387] This intervention is well suited to public service announcements, advertisements, self-teaching, or other brief educational modalities that lack hands-on practice. Emergency dispatchers can provide effective telephone coaching of lay bystanders to provide chest compressions.[388] Responders should perform either hands-only or conventional CPR according to their knowledge, comfort, and training.[7]

Effective rescue breathing requires dedicated learning time and hands-on practice.[224–226] Scaling up rescue breathing to the general public requires access to appropriate personal protective equipment such as valved masks or face shields, but these have been shown to produce high-quality mouth-to-mask or mouth–to–face-shield ventilations in <35% of cases.[389] Program planners aiming to enhance public responses to opioid overdose should carefully consider whether overdose education programs are positioned to provide sufficient effective and evidence-based training on rescue breathing, which requires time and hands-on practice, to enable learners to perform rescue breathing effectively. The complexities of delivering widespread hands-on training on rescue breathing should not impede public education on interventions that do not require hands-on practice such as how to recognize overdose, call 9-1-1, administer naloxone, and perform chest compressions.

- Rescue breathing is challenging to teach and implement broadly. It is sensible to target the significant time and resources required to teach conventional CPR to those portions of the population most likely to attend to OA-OHCA (Table 5).

Telecommunicator Instructions

The 9-1-1 telecommunicator is the first link between the patient and health care. Telecommunicator CPR (T-CPR), also known as telephone CPR or dispatcher-assisted CPR, is a process whereby telecommunicators work with 9-1-1 callers to identify patients with OHCA and coach bystanders to provide CPR before EMS arrival. T-CPR improves bystander treatment and survival after OHCA and is the highest-yield public health intervention for OHCA.[390,391] In the vast majority of OHCA cases, T-CPR protocols deliver compression-only CPR instructions. The rationale for compression-only T-CPR includes ease of 9-1-1 delivery instructions, ease of bystander execution, and low likelihood of bystander



Formula for effective first aid in opioid poisoning and opioid-associated out-of-hospital cardiac arrest

Goal	Intervention	Details	Science and Education	Implementation and socio-political considerations
Identify the emergency and get help	Recognize opioid-related emergencies	Contextual rather than toxidromal definition	PSA and Billboards alerting public for signs of opioid poisoning	Polypharmacy and comorbidity may obscure the opioid toxidrome. Vital signs and pulse checks not reliable.
	Activate emergency services	911	PSA and billboards recommending early activation of EMS	Social marginalization and fear of arrest may impede access to emergency services. Good Samaritan legislation needed.
Treat less critical cases and prevent deterioration to cardiac arrest	Naloxone administration	Intramuscular 0.4mg or intranasal 2-4mg	OEND, THN, dispatcher instructions to administer naloxone	Prescription laws, cost and insurance coverage for naloxone, naloxone kits and proprietary devices may facilitate or inhibit access to naloxone. Policies for refusal to be transported to ED.
	Rescue breathing	Response to asphyxial etiology of opioid-related poisoning.	BLS training with simulation which requires at least 4 hours and periodic recertification	Requires intensive education to perform with minimal efficacy; skill is poorly retained. Implementation requires access to appropriate PPE and rescue breathing barrier and valve or mask devices with poor efficacy.
	Recovery position	Avoid positional obstruction	First aid or BLS education	Unknown effectiveness and educational efficiency.
Improve survival in OA-OHCA	CPR (Hands-Only or Conventional)	No variation from approach to other causes of OHCA	Targeting education in rescue breathing and conventional CPR to those at high risk to witness or experience overdose (**Table 4**)	Efficacy of hands-only CPR demonstrated with brief training and after dispatcher instructions. Conventional CPR appears more effective in non-cardiac OHCA.

Figure 6. Modified Utstein formula for implementation of effective first aid in out-of-hospital cardiac arrest (OHCA).
BLS indicates basic life support; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; OA-OHCA, opioid-associated out-of-hospital cardiac arrest; OEND, overdose education and naloxone distribution; PPE, personal protective equipment; PSA, public service announcement; and THN, take-home naloxone. Reprinted from Søreide et al[382] with permission from Elsevier. Copyright © 2013, Elsevier Ireland Ltd. Published by Elsevier Inc.

refusal.[392] There is a paucity of data on the use of T-CPR to treat OA-OHCA.

The American Heart Association and National Highway Traffic Safety Association have endorsed a 2-question approach (called No, No, Go) for 9-1-1 dispatchers to speed recognition of OHCA permitting initiation of CPR within 60 seconds of a 9-1-1 call.[393] The questions are the following: Is the patient conscious? Is the patient breathing normally? If the answer to both questions is no, the telecommunicator is advised to start compression-only CPR without delay. In the case of opioid overdose, the dispatcher must have a high index of suspicion. In the so-called OA life-threatening emergency, the patient may have respiratory depression, respiratory arrest, or CA.[7] Contemporary data reveal that 16.7% of naloxone administrations by EMS were properly identified a priori as opioid poisoning.[209] Telecommunicator instructions to perform conventional CPR[7] and administer naloxone are validated interventions. Up to 98% of bystanders can correctly administer naloxone after rapid instruction (eg, T-CPR).[394] Because non–health care professionals' ability to accurately determine pulselessness is poor, naloxone may be beneficial in this situation.

- T-CPR instructions to provide compression-only CPR in OHCA have strong support. The ability of dispatchers to correctly identify opioid poisoning is an area where improvement is possible. Such recognition could permit targeted instructions to administer naloxone or perform conventional CPR as appropriate.

Public Access to Opioid Antagonists

Naloxone rapidly and effectively reverses respiratory depression induced by opioids, potentially preventing OA-OHCA. Naloxone is widely carried by EMS personnel.[395] Others (eg, friends, family, bystanders) arriving on scene before EMS can initiate this lifesaving therapy. Untrained bystanders can successfully administer naloxone, and this has been shown to be effective in reducing mortality.[204,396,397] This approach requires that individuals have awareness about when to use naloxone, readily available access to the medication, and willingness to administer.[394] Tactics to increase public naloxone use have included increasing education, reducing barriers to obtaining naloxone from pharmacies, establishing THN programs, placing naloxone in public spaces, and training and equipping laypeople likely to encounter opioid poisonings (Table 5). Policies geared toward increasing naloxone availability should be paired with expanded OUD treatment.[398]

Opioid Education and Naloxone Distribution

OEND programs often focus on early recognition of overdose and training on effective naloxone administration.[397,399–401] Brief education modules are sufficient for

improving overdose recognition and management.[402–404] Educational programs may also provide supplies such as 2 naloxone doses, a naloxone administration device (intranasal atomizer or syringe), gloves, and an instruction card.[397] Adding OEND to first aid courses is reasonable for groups with a high probability of overdose contact such as law enforcement officials, festival and nightclub personnel, and librarians.[381,387]

THN Programs

Provision of naloxone kits is cost-effective, safe, and associated with reductions in overdose deaths.[204,405,406] US and international recommendations support the provision of naloxone kits to laypeople, individuals in substance use programs, patients on high doses of prescription opioids (≥50 mg/d morphine equivalent), and individuals leaving prison.[204,405,407,408] The best way to implement THN and associated overdose recognition and response training at a population level remains a research question. Naloxone dispensing from the ED or other prehospital settings (eg, public health departments, pharmacies, health care facilities, and substance use treatment facilities) may be more effective than prescribing. In 1 ED, <2% of prescriptions for low-cost intranasal naloxone kits were filled from a pharmacy 200 yards from the ED exit.[409] Several community organizations also have developed programs for widely distributing naloxone to individuals with high-risk use and their friends and family members.[206,410–412] The Harm Reduction Coalition[413] regularly surveys organizations providing naloxone kits to laypeople.[414] A report from 2014 demonstrated that there were 644 US THN program sites that dispensed naloxone to >38 000 nonmedical personnel annually.[414] These programs reported an estimated 26 000 overdose reversals.[414] In Canada, naloxone was removed from the Prescription Drug List in 2016, and >590 000 naloxone kits have been distributed across over 8700 sites since 2005. There have been >61 000 reports of naloxone kits used to reverse an overdose.[415] A systematic review of studies from the United States, Canada, and the United Kingdom identified a strong association between THN programs and survival from overdose, with 2336 administrations resulting in 2249 overdose reversals.[202]

Pharmacy

Conventionally, naloxone could be prescribed only to patients with OUD, but over the past decade, most states have expanded their laws to increase access to naloxone.[416,417] State laws permitting pharmacy dispensing of naloxone have been associated with the greatest reductions in death.[418] Prescriber immunity provisions protect prescribers from potential liability and have contributed to reductions in opioid overdoses and deaths.[204,419] Naloxone legislation and standing-order provision have demonstrated an increase in access to naloxone among Medicare recipients.[420] Laws increasing naloxone access for laypeople also have been associated with an increase in the number of naloxone prescriptions dispensed in retail pharmacies[421] and increases in OEND programs.[422] Some programs proactively seek to increase naloxone access in pharmacies,[423] identify patients likely to require naloxone, and prophylactically prescribe it to them.[424] One large pharmacy chain used a 3-pronged approach of providing safe medication disposal kiosks, expanding national access to naloxone, and providing education on the risk and avoidance of opioid overdose.[425] Although barriers still exist to creating universal access to naloxone,[426] it is available in many states under a standing order or over the counter, although it is not stocked at all pharmacies.[418,427]

Opioid Antagonist Public Access Stations

Bystander administration of naloxone in suspected overdose is effective and recommended (Supplemental Figure 1)[7] but requires bystanders to have naloxone access. One solution is to make naloxone publicly available in communities where it is most often needed. Most bystanders are willing to access and administer prestationed naloxone when instructed.[394] There are similarities between this challenge and efforts undertaken for public access to automated external defibrillators. Prior work has described the application of geospatial mapping to identify potential placement of publicly deployed naloxone stations for rapid access by individuals. One retrospective report of 700 EMS deployments that involved opioid overdose or naloxone administration[428] demonstrated that 40% of these occurred within 200 m of potential administration sites, suggesting feasibility in identifying high-risk areas.[428] Placement of naloxone in locations of high risk (eg, high levels of overdose) benefit those areas, but this benefit may not apply to regions with less concentrated risk.[429] In Rhode Island, the publicly accessible NaloxBox contains multiple doses of naloxone and a barrier mask to facilitate rescue breaths. Of 47 sites, none have been vandalized.[430] A prior report investigated the impact of colocating naloxone kits with automated external defibrillators. It was estimated that 16% of naloxone administrations would have been within an estimated walking distance radius of 200 m of an automated external defibrillator location.[431]

- Improving public access to naloxone saves lives by preventing OA-OHCA, yet important questions remain on how to optimize strategies.[377,432]

Public Access to Masks

Providing rescue breathing is a barrier for laypeople given fears of communicable diseases and regurgitation of bodily fluids.[433–436] Lay responders to opioid overdose reported a willingness to provide rescue breaths

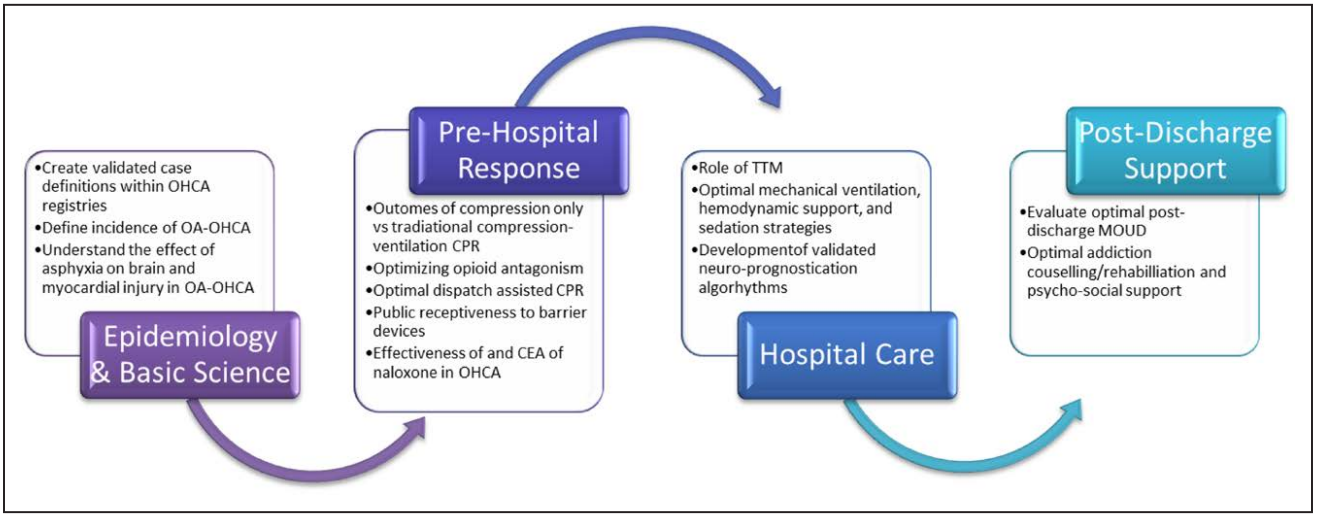


Figure 7. Knowledge gaps and research priorities for opioid-associated out-of-hospital cardiac arrest (OA-OHCA).
CEA indicates cost-effective analysis; CPR, cardiopulmonary resuscitation; MOUD, medication for opioid use disorder; and TTM, targeted temperature management.

in 23% to 66% of cases.[206] Apprehension with rescue breathing has been associated with low overdose response self-efficacy among people who use opioids.[437] Infection-control measures such as barrier devices may reduce the low risk of infectious disease during CPR.[438] Implementation research testing bundled naloxone and conventional CPR education (with barrier masks) demonstrated increased willingness to give rescue breaths.[357,401,439,440]

National Awareness/International Programs

Improving awareness of naloxone and its potential lifesaving ability is of great importance for increasing access and use.[398] For health care providers, specific guidance for improving awareness includes the following:

> *(1) Learning to identify factors that increase patient risk for opioid overdose; (2) following US Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain; (3) making use of prescription drug monitoring programs; (4) finding out whether their state permits pharmacists to prescribe naloxone or dispense it under a standing order (ie, without a patient-specific prescription) or under a collaborative practice agreement; (5) prescribing or dispensing naloxone to individuals who are at an increased risk for opioid overdose and to their friends and family; and (6) determining whether naloxone is covered by insurance or is available at low or no cost to their patients.*[398]

In Australia, THN programs have been in existence since 2012. Using data from a 2013 to 2015 national survey of individuals who inject drugs, most (80%) reported awareness of naloxone, but fewer (52%) reported having heard of THN programs. Less is known about differences in programs or actual use in emergencies.[441] In Vancouver, Canada, a survey of people who inject drugs demonstrated that 68% reported awareness of THN, 19% had witnessed an overdose in the past 6 months, but only 22% had a THN kit.[442] In the United States, state-level public health campaigns have been deployed to improve awareness such as Ohio's "Stop overdose. Carry naloxone." and Project DAWN (Deaths Avoided With Naloxone).[443] Other efforts have focused on opioid prevention on campus and targeted increasing awareness.[444] One college reported a comprehensive approach of stocking naloxone in residence halls and with police, training resident advisors and police to respond to suspected overdose, and engaging student pharmacists in a service program to increase university naloxone access and awareness.[445] The US Department of Veterans Affairs was the first large US health care system to implement an OEND.[446] This effort was rolled out across all (n=142) Veterans Affairs medical facilities. A key component of this program focused on awareness, including development of patient and provider education resources and evaluation resources.[446] A Veterans Affairs study of primary care providers reported improvements in awareness of naloxone kits and CDC recommendations for safe administration of opioids.[447] The use of fentanyl test strips has demonstrated undisclosed fentanyl contamination of heroin more than one-half to three-quarters of the time.[448,449] People who use drugs report a willingness to screen their drugs with fentanyl test strips and modify use to prevent poisoning when fentanyl is detected.[450,451] Thus, fentanyl test strips may represent a tool for harm reduction.

Several reports have evaluated the attitudes of key stakeholders toward increasing access to naloxone and

the concern whether this could have an unintended consequence of increasing opioid use.[452,453] There is no clear consensus on this issue, and data on the impact of increasing naloxone access on relapse rates remain uncertain. More liberal prescription laws on naloxone are associated with increases in nonfatal overdoses presenting to EDs.[418]

- Local and national efforts are underway to improve naloxone awareness among providers, high-risk patients, and the public.

KNOWLEDGE GAPS AND FUTURE RESEARCH

Intertwined with the need for novel implementation science strategies in OA-OHCA is a pressing need to better understand the national and global epidemiology and the distinctive pathophysiology of end-organ injury. We propose that pragmatic first steps could include the development of validated OA-OHCA case definitions that would enable embedding select data points within existing transitional OHCA registries (eg, CARES) and public health initiatives at minimal additional cost. In addition to capturing more accurate prevalence and outcomes, registries could form the foundation for retrospective research inquiries that could better inform our treatment of the disease, care, or treatment gaps. These efforts could ultimately lead to quality improvement initiatives or prospective trials that could advance processes of care and survival. An outline of potential research priorities in this field is presented in Figure 7. Our group felt that the highest-priority items for future research in OA-OHCA included studying how naloxone should be used during resuscitation, defining novel brain injury pathways and protective agents, defining the risks and benefits of compression-only versus conventional CPR, determining optimal education and implementation, studying the best interventions, and establishing policies for preventing subsequent mortality after opioid poisoning.

CONCLUSIONS

The present opioid epidemic has increased OA-OHCA, which is distinct in pathophysiology from cardiac-type OHCA. Whether these pathophysiological differences require modifications in prehospital and posthospital management requires further research in areas such as the impact of naloxone during CPR and conventional compared with compression-only CPR. Targeted educational campaigns providing OEND and conventional CPR training to those likely to have or witness an opioid overdose will likely prevent and optimally treat cases of OA-OHCA. Along with broader public education, legal reforms and policy aimed at preventing OA-OHCA can save lives and provide links to medication treatment and recovery of a generally young, otherwise healthy segment of our population.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Writing group member	Employment	Research Grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Owner-ship interest	Consultant/advisory board	Other
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Saket Girotra	University of Iowa Carver College of Medicine	VA ORH (grant on PAD)†	None	None	None	None	None	None
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Raina M. Merchant	University of Pennsylvania	NIH R21: analyzing online reviews to evaluate quality of care at substance use disorder treatment facilities*	None	None	None	None	None	None
Aaron M. Orkin	University of Toronto Institute of Health Policy, Management & Evaluation (Canada)	Adapt Pharma (provides in-kind donation of a naloxone delivery to the SOONER Project, a design project and randomized controlled trial on which he is a coinvestigator)*; Canadian Institutes of Health (SOONER [Surviving Opioid Overdose With Naloxone] Project)*	American Red Cross (member of the ARC Scientific Advisory Committee)*	None	Ontario Office of the Chief Coroner investigation concerning a death related to opioid overdose*	None	None	None
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*Modest.

†Significant.

‡Now with Baylor College of Medicine.

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Andrew A. Monte	University of Colorado School of Medicine	None	None	None	None	None	None	None
Juan C. C. Montoy	University of California, San Francisco	SAMHSA (Evaluator on an implementation project funded by SAMHSA. The PIs [Vo, Mercer] have begun a naloxone distribution program that is led primarily by EMS. Grant 1 H79 SP080315-01)†	None	None	None	None	None	None
Brian Reed	Rockefeller University	None	None	None	None	None	None	None

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†Significant.

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