Circulation

AHA PRESIDENTIAL ADVISORY

Opioid Use and Its Relationship to Cardiovascular Disease and Brain Health

A Presidential Advisory From the American Heart Association

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ABSTRACT: The misuse of opioids continues to be epidemic, resulting in dependency and a recent upsurge in drug overdoses that have contributed to a significant decrease in life expectancy in the United States. Moreover, recent data suggest that commonly used opioids for the management of pain may produce undesirable pharmacological actions and interfere with critical medications commonly used in cardiovascular disease and stroke; however, the impact on outcomes remains controversial. The American Heart Association developed an advisory statement for health care professionals and researchers in the setting of cardiovascular and brain health to synthesize the current literature, to provide approaches for identifying patients with opioid use disorder, and to address pain management and overdose. A literature and internet search spanning from January 1, 2012, to February 15, 2021, and limited to epidemiology studies, reviews, consensus statements, and guidelines in human subjects was conducted. Suggestions and considerations listed in this document are based primarily on published evidence from this review whenever possible, as well as expert opinion. Several federal and institutional consensus documents and clinical resources are currently available to both patients and clinicians; however, none have specifically addressed cardiovascular disease and brain health. Although strategic tools and therapeutic approaches for recognition of opioid use disorder and safe opioid use are available for health care professionals who manage patients with cardiovascular disease and stroke, high-quality evidence does not currently exist. Therefore, there is an urgent need for more research to identify the most effective approaches to improve care for these patients.

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Key Words: AHA Scientific Statements ■ analgesics, opioid ■ brain ■ cardiovascular diseases ■ guideline ■ opioid-related disorders ■ stroke

The writing committee was composed of physicians, scientists, and a pharmacist with expertise and knowledge in emergency medicine, clinical practice, and research in the management of opioids and opioid use disorder (OUD), federal regulation of opioids, outpatient management of opioids, OUD, and pharmacotherapy in cardiovascular disease. As an American Heart Association (AHA) presidential advisory, this article included Ivor J. Benjamin, MD, as one of the authors with methodological expertise. The committee also included representatives from the AHA councils on Clinical Cardiology; Lifelong Congenital Heart Disease and Heart Health in the Young; Quality of Care and Outcomes Research, Epidemiology and Prevention; and Cardiopulmonary, Critical Care, Perioperative and Resuscitation.

BACKGROUND

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In the United States in 2018, 67 367 people died of drug overdoses, which is a 4.1% decline from the prior year (70 237 deaths).[1] The national age-adjusted death rate attributable to drug overdoses had more than tripled from 6.1 per 100 000 people to 21.6 per 100 000 people from 1999 to 2019[2] and continued to rise in 2020, with the annual number of deaths increasing by 15.5% from December 2019 through June 2020 according to provisional results reported by the National Center for Health Statistics.[3,4] The opioid epidemic has disproportionately affected people in the 25- to 34-year (38.4 per 100 000), 35- to 44-year (39.0 per 100 000), and 45- to 54-year (37.7 per 100 000) age groups.[5] Approximately

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2 of every 3 deaths resulting from drug overdoses involved opioids.[2] Significant variation across US counties and states has been noted,[6] with age-adjusted drug overdose deaths highest in West Virginia (51.5 per 100 000), Delaware (43.8 per 100 000), Maryland (37.2 per 100 000), Pennsylvania (36.1 per 100 000), Ohio (35.9 per 100 000), and New Hampshire (35.8 per 100 000) in 2018.[1] Ongoing concerns have been compounded by rises in opioid-related mortality in >40 states during the recent coronavirus disease 2019 (COVID-19) pandemic[7] and a rise in overall US overdose mortality during the period of March through May, highlighted by the US Centers for Disease Control and Prevention in a public health advisory.[8]

The AHA's 2024 goals are to advance cardiovascular health for all, including identifying and removing barriers to health care access and quality. Deaths resulting from drug overdoses, which are often in younger age groups, continue to drive down the average life expectancy in the United States.[9] The AHA recognizes that it must work together with key stakeholders to address opioid use, including educating the public, improving prescribing practices by health care professionals, promoting early diagnosis and treatment of addiction, and educating the public and health care professionals about the acute care of opioid-related overdoses.

One example of the AHA's long-standing commitment to addressing the opioid epidemic is its global leadership in cardiopulmonary resuscitation (CPR) training, with millions of health care professionals and community members trained each year in lifesaving CPR and first aid education. Opioid overdose, without quick action by bystanders, prompt activation of 9-1-1, and rapid care by lay responders, will result in respiratory arrest.[10] Therefore, public education and awareness of the opioid epidemic must include information and training on opioid overdose and reversal agents (eg, naloxone), activation of the chain of survival by calling 9-1-1, prompt response by first responders, provision of CPR and use of an automated external defibrillator, and evidence-based care of patients with respiratory and cardiac arrest in emergency department and other care settings.[11] AQ6

The AHA has a significant role in addressing this national epidemic and is committed to (1) increasing education and awareness about the risks of opioids and appropriate prescribing by health care professionals; (2) supporting continued research on opioids and their effects on the heart, brain, and overall cardiovascular health and disease; (3) improving methods for automated, real-time data surveillance to track opioid overdoses; (4) advocating to destigmatize OUD and to increase access to lifesaving treatments (eg, naloxone and substance use disorder treatment); and (5) partnering with the general public, governmental agencies, nongovernmental organizations (including health system organizations), and employers to raise awareness of the opioid epidemic.

The recommendations and suggestions/considerations listed in this document are evidence based whenever possible. A review of the literature published from January 1, 2012, until February 15, 2021, was conducted, with references selected as appropriate. Searches were limited to epidemiology studies, reviews, consensus statements, guidelines, and other data conducted in human subjects and published in English.

Science of Opioid Use for Pain Management

Opium contains alkaloids such as morphine and codeine that are ligands of the *mu*-opioid receptor and has been used for thousands of years for the medical management of pain. In the cardiovascular and cerebrovascular systems, opioids and endogenous derivatives such as endorphins exert potent effects within the central and peripheral nervous systems to regulate blood pressure, heart rate, and even thermogenesis in brown adipose tissue. Activation of *mu*-opioid receptors in the dorsal horn of the spinal cord and brainstem descending inhibitory pathway is associated with antinociceptive, nitric oxide–dependent vasodilatory, and hyperthermogenic effects. Although heroin is an analog of morphine, it is hydrolyzed to both morphine and 6-monoacetylmorphine, a metabolite characterized by enhanced and rapid penetration of the blood-brain barrier. It is the combined effect of morphine and 6-acetylmorphine metabolites that is likely responsible for the high relative potency of heroin compared with other opioids.[12,13] Other agents such as hydromorphone, hydrocodone, oxymorphone, and fentanyl have been developed and are commonly used in contemporary clinical practice. Opioids differ from other analgesics by reducing pain perception rather than antagonizing the transmission of pain. Although sensory transmission remains intact, the subjective interpretation of pain is affected and may contribute to interpatient variability during clinical assessment.[12]

History of Prescription Opioid Use in the United States

Although prescription opioids have been used since the 1700s to treat pain, an anecdotal report in 1980 citing a seemingly apparent low rate of addiction among hospitalized patients treated with opioids challenged the practice of using opioids for only relief of acute pain.[14] This report, combined with aggressive pharmaceutical marketing to physicians,[15] pharmaceutical innovations,[16] withdrawal from the market of nonopioid analgesics,[17] initial development of pain management standards supporting routine prescribing of opioids in the hospitalized

patient,[18] pain gradually becoming regarded as the fifth vital sign, and a failure of the clinical professions to demand or develop high-quality evidence,[19] resulted in a steady increase in opioid prescribing that did not plateau until after 2011.

In 2019, the total number of individuals in the United States ≥12 years of age who were using prescription opioids was roughly 82.6 million.[20]

Of this total, 9.7 million prescription opioids were considered misused (prescribed for themselves or for someone else), which represented a significant decrease from the 11.1 million misused opioids in 2017.[7,21] Heroin use was found to be prevalent in 745 000 individuals, with the majority (404 000 individuals) using heroin and also misusing prescription opioids.[22] As prescription opioid use and deaths leveled off, fatalities from illicit and synthetic opioid agents continued to rise.[2,5,23] This increase in overdose death rates is based largely on increases in illicitly manufactured synthetic opioids (ie, fentanyl and fentanyl-related substances), either alone or in combination with other addictive substances such as stimulants and benzodiazepines, which could also impact cardiovascular and brain health.[5,24] Therefore, ensuring that these individuals are identified and treated for all substance use disorders is critical.

Prevalence and Treatment of OUD

In 2018, opioid analgesic misuse was prevalent in 3.4% of women and 3.9% of men in the United States. An estimated 1.7 million Americans had OUD related to opioid analgesics, and 526 000 had heroin-related OUD in 2018.[21,22] However, <30% of individuals with OUD received treatment in the past year.[21,25]

The prevalence of OUD in outpatient clinical care settings has not been assessed to date, but health care professionals can help to identify, assess, and treat OUD or refer patients for treatment.[26] The US Preventive Services Task Force released draft recommendations supporting screening for all illicit drug use in adults, including nonmedical use of prescription drugs,[27] and the 2018 US Surgeon General's Spotlight on Opioids adds that OUD should be systematically addressed, similar to other serious chronic health conditions such as cardiovascular disease.[25] Health care practices may use validated tools[28] such as the Tobacco, Alcohol, Prescription Medication, and Other Substance Use tool[29] to screen patients for opioid misuse annually and to refer patients who screen positive for more thorough assessment and treatment.[26]

Referral to opioid treatment health care professionals is also encouraged.[25] There are efforts to support provision of medications for OUD in order to improve treatment access and to ensure that OUD is treated like other chronic medical conditions. Ideally, cardiologists, neurologists, vascular medicine physicians, and pharmacists would help identify patients with OUD and work in collaboration with their primary care professionals or substance use disorder specialists. For the inpatient and outpatient settings, the establishment of institutional, multidisciplinary panels of stakeholders, including health care professionals and volunteer patient representatives, could leverage expertise, trust, and shared-decision making toward patient-centered prescribing practices, strategies to engage patients with OUD and to promote medications for OUD, and communal remedies for the opioid crisis.

ACUTE MANAGEMENT OF PAIN IN PATIENTS WITH CARDIOVASCULAR DISEASE

Specific Considerations of Opioid Use in Patients With Cardiovascular Disease

The medical utility of opiates has evolved over time. Opioids such as morphine are sometimes used in the cardiovascular setting to reduce pain, anxiety, and sympathetic activity and for venodilation.[14] However, there is also potential to adversely affect outcomes for patients with acute coronary syndrome (ACS).[30] The potential for drug interactions on outcomes has recently been investigated. Because opioids are associated with delayed gastrointestinal motility in healthy subjects,[30] the onset of oral $P2Y_{12}$ receptor antagonists such as clopidogrel also can theoretically be delayed, thereby slowing the onset of action of antiplatelet activity and reducing platelet disaggregation during ACS. The clinical impact of this morphine–$P2Y_{12}$ receptor antagonist drug interaction on mortality in the setting of percutaneous coronary intervention remains unclear according to conflicting reports from large-scale registry data.[31,32] Until further randomized clinical evidence becomes available, a more cautious approach should be taken when balancing the risk and benefits of morphine.[33-35] Therefore, routine pain management in clinical settings should aim to use the lowest effective opioid dosages along with definitive interventions for ACS. In addition, parenteral antiplatelet agents can be considered an alternative during coadministration of morphine in the hospitalized patient with ACS.[36]

Acetaminophen and nonacetylated salicylates are recommended and preferred over cyclooxygenase-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease requiring chronic analgesia.[37] Although tramadol was also recommended in ACS guidelines for short-term musculoskeletal pain, this approach should now be reconsidered given an action by the US Food and Drug Administration (FDA) in 2014 to reassign this agent as an opioid and Schedule IV controlled substance on the basis of potential for abuse and dependence.[38]

Other analgesics considered second-tiered alternatives such as selective cyclooxygenase-2 inhibitors (eg, celecoxib) and nonselective nonsteroidal anti-inflammatory drugs used to treat chronic musculoskeletal pain also should be carefully assessed in patients with cardiovascular disease given an established increased dose-related risk of mortality with these agents. Although previous data suggested that naproxen was likely the safest of all cyclooxygenase-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs in this patient population, a recent randomized noninferiority study found celecoxib to have cardiovascular risks similar to those of nonselective nonsteroidal anti-inflammatory drugs in patients requiring chronic pain management.[39,40] Differences between individual agents in terms of renal function and blood pressure were variable and warrant further study.

Postoperative Pain Management for Interventional and Surgical Treatment of Cardiovascular Disease, Stroke, and Peripheral Artery Disease

Cardiologists, surgeons, neurologists, anesthesiologists, vascular physicians, pharmacists, physician assistants, and nurses should routinely consider postsurgical or postprocedural pain and pain management. Transradial access for percutaneous interventions has increasingly replaced transfemoral approaches for vascular procedures, thereby reducing vascular complications and improving patient comfort.[41] To address opioid overprescribing after surgery, several societies, including the American Pain Society and the American Society of Anesthesiologists, have developed recommendations for the management of postoperative pain.[42] Likewise, both state agencies[43] and consensus expert panels have issued recommendations for the appropriate use of opioids after specific surgical procedures.[44] However, wide variations in prescribing practices, inconsistencies in national guidelines, and variability in the invasiveness of surgical procedures, anatomic sites, mechanism of pain, and perceived pain intensity have contributed to inadequate guidance of procedure-specific opioid treatment after surgery.

Suggestions/Considerations for Acute Management of Pain in Cardiovascular Disease

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On the basis of evolving perspectives and currently published data, our writing group has developed further considerations for clinicians who manage pain in patients with cardiovascular disease.

1. As alternatives to opioids, acetaminophen, aspirin, and nonacetylated salicylates should be considered first in patients with musculoskeletal disease and cardiovascular disease.
2. The routine use of morphine in the setting of ACS may adversely reduce the therapeutic efficacy of $P2Y_{12}$ receptor antagonists.
3. Morphine can be useful to reduce acute pain and anxiety when used in moderation in patients who continue to experience pain despite alternative approaches.
4. Parenteral antiplatelet agents for ACS can be considered when coadministered with morphine in the hospitalized setting.
5. Research is needed to identify new approaches to improve availability and access to nonpharmacological pain treatment options.

Sequelae of OUD: Considerations of Treatment of Infective Endocarditis

A well-established potential consequence of injection of opioids in general is infective endocarditis (IE).[45] The opioid epidemic has resulted in a 12-fold increase in the incidence of hospitalizations for endocarditis in drug-dependent patients since 2010 in North Carolina,[46] and a connection between increasing rates of invasive methicillin-resistant *Staphylococcus aureus* infections and injection drug use, including opioid injection, has been identified.[47] In addition, hospitalization rates for strokes from cerebral emboli associated with IE and opioid use increased sharply in 2008 compared with the previous 2 decades.[45] The most recent AHA scientific statement on IE was published in 2015.[48] The importance of guideline-based care of IE, stroke, and other IE-related cardiovascular complications, coupled with medical management of opioid misuse and addiction, cannot be overstated.

Education and Training of Health Care Professionals and Lay Responders in the Acute Management of Opioid Overdose

The AHA has guidelines for both health care professionals and lay responders on how to provide basic life support (Figures 1 and 2) for a person with a suspected opioid overdose.[49] An emphasis is placed on activating 9-1-1 quickly, initiating chest compressions immediately, administering naloxone (a competitive opioid antagonist), and implementing an automated external defibrillator. The guidelines also provide recommendation for different levels of patient responsiveness and breathing (Table 1). In 2019, the AHA responded to the opioid epidemic and need for more advanced training by creating 2 courses for clinical staff (eg, health care professionals) and nonclinical staff/lay responders.[50] The AHA continues to partner with community, local, and national organizations to increase awareness and to improve response to opioid overdose.

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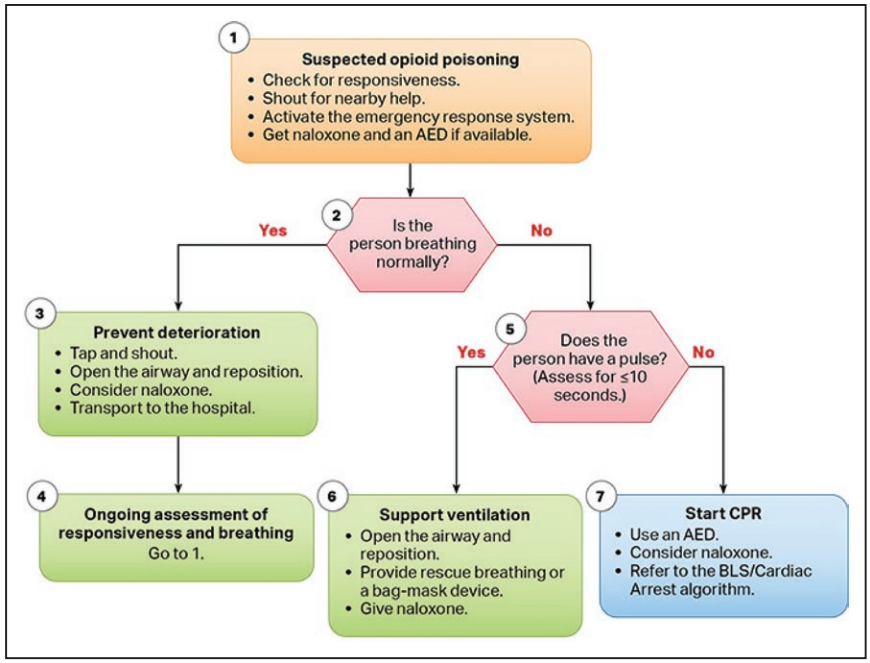

Figure 1. Opioid-associated emergency for the health care professional algorithm.
AED indicates automated external defibrillator; BLS, basic life support; and CPR, cardiopulmonary resuscitation. Reprinted from Panchal et al.[49] Copyright 2020 American Heart Association, Inc.

There are some differences between AHA guidelines and community-based instructions: (1) when to engage emergency services and the use of rescue breathing and (2) the time frame of repeat naloxone administration. AHA recommendations align with early community-based program instructions to seek emergency 9-1-1 assistance before naloxone administration. The focus is on supporting the airway and breathing first (with rescue breaths if possible), activating the emergency response system early, and providing high-quality CPR. The AHA emphasizes phoning 9-1-1 and initiating CPR before naloxone administration because it may be difficult, especially for the lay rescuer, to identify the underlying cause of the cardiac arrest, and naloxone would be effective only if the person's cardiac arrest were caused by an opioid overdose. The instructions provided in the FDA-approved autoinjector and nasal spray formulations recommend the reverse order (give naloxone and then phone 9-1-1), which should be the preferred approach when opioid overdose is certain. Other community-based program instructions more practically endorse whichever approach can be done most quickly first. Second, the AHA recommends that if recurrent opioid toxicity develops, repeated small doses or an infusion of naloxone can be beneficial, but a time interval is not specified. However, repeat administration every 2 to 3 minutes with the autoinjector[51] and nasal spray formulation[52] is recommended by the FDA in addition to recent community-based instructions if further guidance is needed.[53]

Suggestions/Considerations for the Acute Management of Opioid Overdose

1. Ensure that all public health education and training programs addressing suspected opioid overdose include basic instructions for calling 9-1-1, performing CPR with rescue breathing, using an automated external defibrillator, and administering naloxone.
2. Leverage the successes of the AHA's broad-scale efforts in CPR and resuscitation to increase awareness and education of patients and health care professionals in the prevention, screening, and training of opioid overdose response.

The AHA's Workplace Health Initiative

Employers have an important role to play in addressing opioid use and misuse. The roughly 164 million adults in the US workforce[54] spend many of their awake hours weekly at work. In addition, 58.4% of the nonelderly population was covered by employer-sponsored health insurance plans in 2017.[55] The workplace can provide insight into opioid misuse; thus, employers can play a role in addressing opioid use. The National Institute for Occupational Safety and Health has information and links on its website related to opioid use in the workplace.[56] In response to the challenges of opioid misuse, the American Association of Occupational Health Nurses has published a position statement because the misuse of opioids and the opioid crisis in general can have a significant impact in the workplace that can be addressed, in part, by occupational nurses who are in the workplace.[57] The AHA's CEO Roundtable released a leadership pledge in 2018 to tackle the opioid epidemic by encouraging business leaders to confront the opioid crisis by employers working with their employee health plans, pharmacy benefit managers, and employee assistance programs to adopt science-based policies and strategies to reverse national trends.

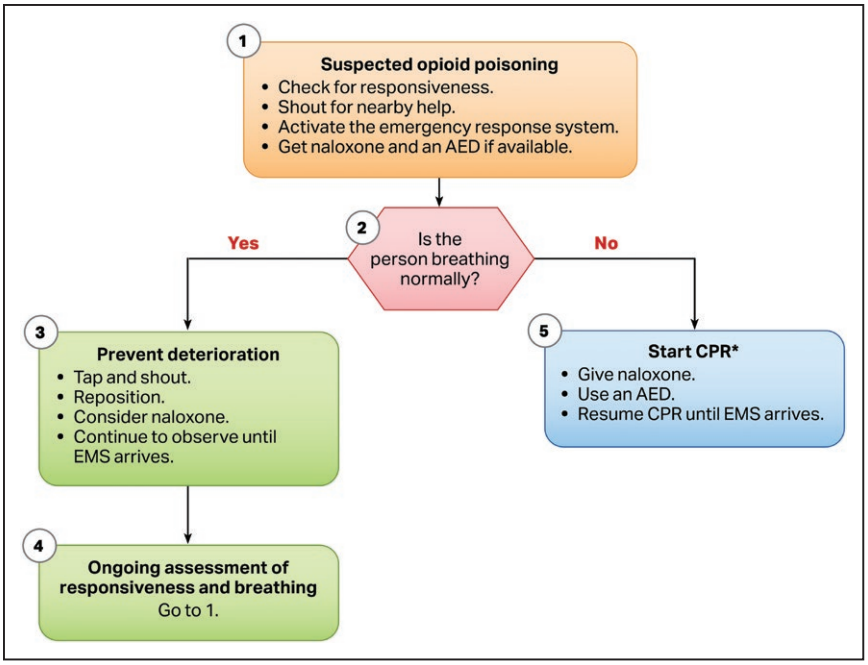

Figure 2. Opioid-associated emergency for lay responders algorithm.
AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; and EMS, emergency medical service. *For adult and adolescent victims, responders should perform compressions and rescue breaths for opioid-associated emergencies if they are trained and perform hands-only CPR if not trained to perform rescue breaths. For infants and children, CPR should include compressions with rescue breaths. Reprinted from Panchal et al.[49] Copyright 2020 American Heart Association, Inc.

Suggestions/Considerations for the Workplace

1. Health care professionals who manage pain in the setting of cardiovascular and stroke should be encouraged to receive training in evidence-based nonopioid pain management strategies and OUD screening.
2. The number of health care professionals who can prescribe medications for OUD should be increased, and treatment with medications that have been shown to decrease morbidity and mortality in patients with OUD should be destigmatized (eg, align with other chronic health conditions that have effective medication regimens).
3. Employers are encouraged to adopt science-based policies and strategies to reverse national trends.

PROMOTING PARTNERSHIPS IN COMBATTING THE OPIOID PUBLIC HEALTH CRISIS

Contemporary Federal and Institutional Approaches to Opioid Abuse in the United States

In the face of the opioid crisis, numerous strategies have been put forth to address safety concerns for 2 main populations affected by the crisis: individuals using prescription opioids and individuals using illicit opioids. Addressing the needs of these diverse populations has required efforts spanning public health, health care, law enforcement, and community organizations, among others. The multiple approaches advocated by national, state, and local organizations are summarized in Table 2.

Compton and Jones[6] provide a framework for understanding the US opioid crisis from an epidemiological perspective, proposing a host-agent-vector-environment model with vector added to the standard host-agent-environment approach as a way to underscore the active role of opioid purveyors (eg, pharmaceutical industry, prescribing clinicians, illicit opioid sellers) and implementing other approaches that may help improve health outcomes (Figure 3). They highlight the importance of 5 strategies: (1) health care professional education, training, and guidance, including deployment of clinical tools such as prescription drug monitoring programs and academic detailing; (2) primary prevention of substance use, including opioid misuse; (3) expansion of medication treatment for OUDs, particularly including access by vulnerable groups, including those in criminal justice, inpatient, outpatient, and emergency care settings; (4) naloxone prescription as part of opioid treatment and increased overall naloxone access and use as part of comprehensive rescue and resuscitation; and (5) comprehensive syringe service programs and other

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Table 1. Differences in Response to Opioid Overdose for the Lay Responder[50]

If the patient is…	Do this:
Responding and breathing	Phone 9-1-1 and get naloxone and an AED if available
Not responding but breathing	Phone 9-1-1, tap and shout, reposition, and consider giving naloxone
Not responding and not breathing or only gasping	Phone 9-1-1, start CPR, give naloxone, and use an AED

AED indicates automated external defibrillator; and CPR, cardiopulmonary resuscitation. Reprinted from Reference 50. Copyright 2020 American Heart Association, Inc.

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Table 2. Key Federal Approaches to Addressing the Opioid Public Health Crisis

Key stakeholder	Priorities	Source for information
Department of Health and Human Services[58]	(1) Access: better prevention, treatment and recovery services; (2) data: better data on the epidemic, (3) pain: better pain management; (4) overdoses: better targeting of overdose reversing drugs; and (5) research: better research on pain and addiction	Help and Resources: National Opioids Crisis[59]
National Institutes of Health	Research priorities targeting (1) improving prevention and treatment for opioid misuse and addiction–novel medication options for OUD and overdose, enhanced outcomes for infants and children exposed to opioids, new strategies to prevent and treat opioid addiction, translation of research to practice for the treatment of opioid addiction–and (2) enhancing pain management–preclinical and translational research in pain management and clinical research in pain management	NIH HEAL Initiative Research Plan[60]
Centers for Disease Control and Prevention[61]	Developing and promoting a public health response: (1) conduct surveillance and research; (2) build state, local, and tribal capacity; (3) support health care professionals, health systems, and payers; (4) empower consumers to make safe choices; and (5) partner with public safety	CDC's Response to the Opioid Overdose Epidemic[62]
National Academies of Medicine[63]	Action collaborative on countering the US opioid epidemic, including multiple working groups and publications, such as (1) Medications for Substance Use Disorders Save Lives; (2) Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and the Risks of Prescription Opioid Use; (3) Integrating Responses at the Intersection of Opioid Use Disorder and Infectious Disease Epidemics: Proceedings of Workshop; (4) First, Do No Harm: Marshaling Clinician Leadership to Counter the Opioid Epidemic; (5) Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public-Private Partnerships: Proceedings of a Workshop; (6) Pain Management and Prescription Opioid-Related Harms: Exploring the State of the Evidence: Proceedings of a Workshop in Brief; (7) Pain Management for People With Serious Illness in the Context of the Opioid Use Disorder Epidemic; and (8) Medication-Assisted Treatment for Opioid Use Disorder	National Academies of Sciences, Engineering, and Medicine. 2017. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24781[64]
Substance Abuse and Mental Health Services	Multiple service delivery and communication efforts to improve the prevention and treatment of opioid misuse, addiction, and overdose, including (1) state targeted response and state opioid response grants ($2.5 billion across fiscal years 2017–2019); (2) support for evidence-based prevention/education/treatment/recovery services; (3) enhanced naloxone access by first responders and peers ($49 million in fiscal year 2019); (4) medication-assisted treatment, prescription drug, and opioid addiction targeted grants ($89 million in fiscal year 2019); (5) treatment for pregnant and postpartum women and infants with neonatal abstinence syndrome ($29.9 million in fiscal year 2019); (6) criminal justice–based medication-assisted treatment, targeting drug courts and offender reentry into the community ($89 million in fiscal year 2019); (7) building communities of recovery ($6 million in fiscal year 2019); (8) Reinstatement of the Drug Abuse Warning Network surveillance system ($10 million in fiscal year 2019); and (9) surveillance and program data, including the National Survey on Drug Use and Health	The Opioid Crisis: Next Steps[65]
Veterans Health Administration	Comprehensive efforts using 4 broad strategies: (1) education, (2) pain management, (3) risk mitigation, and (4) addiction treatment	Gellad et al, "Addressing the Opioid Epidemic in the United States: Lessons From the Department of Veterans Affairs"[66]
FDA	Priorities include (1) decreasing exposure to opioids and prevent new addiction through product labeling, storage/disposal, and health care professionals education; (2) supporting the treatment of those with OUD, including both medication-assisted treatment for OUD and naloxone for overdose; (3) fostering the development of novel pain treatment therapies through partnerships; and (4) improving enforcement and assessing benefit-risk balance	Throckmorton, "Search for Balance: FDA's Approach to the Opioids Crisis"[67]

CDC indicates Centers for Disease Control and Prevention; FDA, US Food and Drug Administration; HEAL, Helping to End Addiction Long-Term; NIH, National Institutes of Health; and OUD, opioid use disorder.

harm reduction programs. They also emphasize that efforts to constrain opioid prescribing should include appropriate tapering protocols and access to nonopioid pain treatments (Table 3).[74] The need for appropriate tapering protocols and access to nonopioid pain treatments are especially important given research suggesting elevated overdose and suicide mortality rates after prescription opioid cessation.[75] The Department of Health and Human Services has released a guide to assist with tapering or discontinuation of long-term opioid analgesics, emphasizing the importance of avoiding abrupt discontinuation or dosage reduction when possible.[74]

Regulatory Considerations and Role of Regulatory Bodies

The spectrum of opioid use, pain management, and treatment of addiction and overdose involves a complex morass of regulation. In the United States, the approval of opioids for marketing and its advertising are governed by the FDA, and the overall supply of opioids to the market-

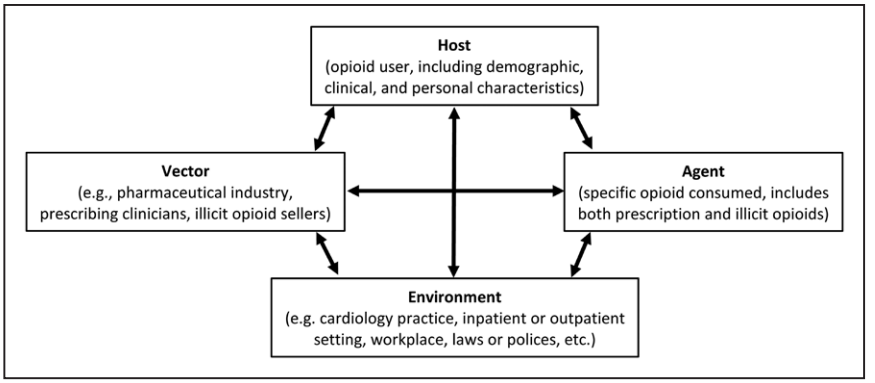

Figure 3. The host-agent-vector-environment model[6] of factors involved in opioid misuse.
Reprinted from Compton and Jones.[6]

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place is governed by the Drug Enforcement Administration of the Department of Justice. All drug control efforts are coordinated by the White House Office of National Drug Control Policy, including prevention, treatment, and law enforcement activities. Prescribing of opioids is governed by state regulatory agencies overseeing the practice of medicine; local dispensing, by state pharmacy boards.

In 2017, the FDA asked the National Academies of Sciences, Engineering, and Medicine to convene a committee to update the state of the science on pain research, care, and education and to identify actions that the FDA and others can take to respond to the opioid epidemic. The key question was how to weigh the societal risks of addictive substances relative to the benefit-risk balance for the individual. The recommendations provide the basis for a new regulatory paradigm for opioids, with a particular focus on informing the FDA's development of a formal method for incorporating individual and societal considerations into its risk-benefit framework for opioid approval and monitoring.[76]

Training on prescribing is a common goal. For instance, because of the unusual risk associated with opioid prescribing, the FDA instituted a risk evaluation and mitigation strategy plan for all opioids. Although some evidence of the effectiveness of this program has been produced,[77-79] calls for a more impactful risk evaluation and mitigation strategy and evidence casting doubt on the program persist.[80] Medical societies have resisted mandatory training until recently, but many states now require it, and as of July 1, 2019, the Accreditation Council for Graduate Medical Education has required that all graduate medical education programs "provide instruction and experience in pain management if applicable for the specialty including recognition of the signs of addiction."[81] The AHA recommends that all clinicians caring for patients with cardiovascular disease participate in continuing education to document knowledge and skills in the detection and prevention of OUD and in the treatment of acute and chronic pain, including opioid prescribing and non-opioid pain management. As described, referral to effective treatment that can include medications for OUD is essential; however, significant local effort is needed to ensure that adequate numbers of qualified clinicians, facilities, and social services are available (Figure 4). Perhaps most important, the evidence base for this field is a fraction of the evidence base for standard cardiovascular disease prevention and treatment. The AHA strongly urges clinicians to participate in research that will inform policymakers to improve the regulatory regimens with high-quality evidence.

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Suggestions/Considerations for Addressing the Opioid Public Health Crises

1. Expansion of syringe service programs should be considered to reduce the risk of endocarditis.
2. The FDA's approach for considering societal impact in addition to the individual risk-benefit balance when regulating opioids should be finalized.
3. Harmonization of approaches among federal agencies and across states should be improved.
4. Risk evaluation and mitigation strategy educational programs should continue to be improved.
5. Clinical pain and addiction training requirements should be implemented and their effective assessed.
6. Focused education and training of health care professionals in opioid tapering protocols and nonopioid alternatives should be initiated.

RESEARCH GAPS

Gaps in Science Related to Cardiovascular Disease

The tremendous impact of pain, opioid addiction, and overdose reveals an enormous gap in knowledge that needs to be filled by basic, translational, clinical, and implementation research. Given the immediate and dramatic loss of life and function, it is essential to guide current preventive and therapeutic efforts with

Table 3. Approaches in Addressing the Opioid Public Health Crisis

Level of action	Approach	Examples of evidence-based approaches decreasing opioid deaths in the United States and Sources
State and county-based Departments of Health	Data surveillance of opioid overdoses (fatal and nonfatal)	
	PDMP management and use	Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States[68]
	Implement syringe service programs to reduce risks and to increase treatment engagement	
Health care professionals	Education and training on management of opioid overdose	AHA basic life support and advanced cardiac life support courses
		AHA health care professional opioid course
	Safer prescribing and tapering of opioids	HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics[69]
		Pocket Guide: Tapering Opioids for Chronic Pain[70]
		FDA Identifies Harm Reported From Sudden Discontinuation of Opioid Pain Medicines and Requires Label Changes to Guide Prescribers on Gradual, Individualized Tapering[71]
	Highlight alternative treatment options for pain management	
	Increase access to medications for OUD	
	PDMP utilization Academic detailing	Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States[68]
Health care systems	Develop comprehensive approaches to identify patients at risk for OUD and use systems-based approaches to improve opioid safety and pain management	Veterans Health Administration Opioid Safety Initiative
	Expanded access to medications for OUD	National Academies of Science, Engineering, and Medicine, *Medications for Opiod Use Disorder Save Lives*[72]
Health insurers	Eliminate prior authorization requirements for medications for OUD	Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States[68]
Retail pharmacies, clinics, and schools of pharmacy	Potential for practice, research, and education	Compton et al, "Promising Roles for Pharmacists in Addressing the U.S. Opioid Crisis"[73]
Law enforcement	Adopt Good Samaritan Laws to encourage bystanders to call 9-1-1 after an overdose (ie, minimize their own risk of arrest)	Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States[68]
Community-based organizations	Reduce stigma of addiction treatment	
	Targeted naloxone distribution	
	Resources for addiction treatment and counseling	

AHA indicates American Heart Association; FDA, US Food and Drug Administration; HHS, US Department of Health and Human Services; OUD, opioid use disorder; and PDMP, Prescription Drug Monitoring System.

clinical and implementation research while conducting basic and translational research to better understand opioid biology and addiction and to develop new and more effective therapies for pain. Readers are referred to the National Science and Technology Council's report "Health Research and Development to Stem the Opioid Crisis,"[82] which provides a comprehensive recitation of research gaps that have been identified, and the National Institutes of Health's Helping to End Addiction Long-Term Initiative,[83] which describes a comprehensive plan for clinical and translational research.[84]

The AHA has a direct interest in the biology of addiction in general. Better understanding of the basic biology of addiction could lead to improved approaches to prevent addiction and to treat it effectively. Of particular interest would be the understanding of similarities and differences in addiction pathways associated with opioid, stimulant, alcohol, and nicotine addiction. Because clinicians caring for patients with cardiovascular disease use opioids for treatment of pain, specific research to conduct comparative-effectiveness trials of available opioid alternatives and the development of novel nonopioid medicines or opioid ligands that can produce analgesia without triggering addiction should take priority. An area of research that has received little attention is the cardiovascular manifestations of opioid withdrawal and therapeutic approaches to preventing them. Other specific areas of importance to cardiovascular medicine are the comparative effectiveness of different approaches to periprocedural pain and the pain and anxiety associated with acute catastrophic cardiovascular emergencies such as ACS, heart failure, and pulmonary edema.

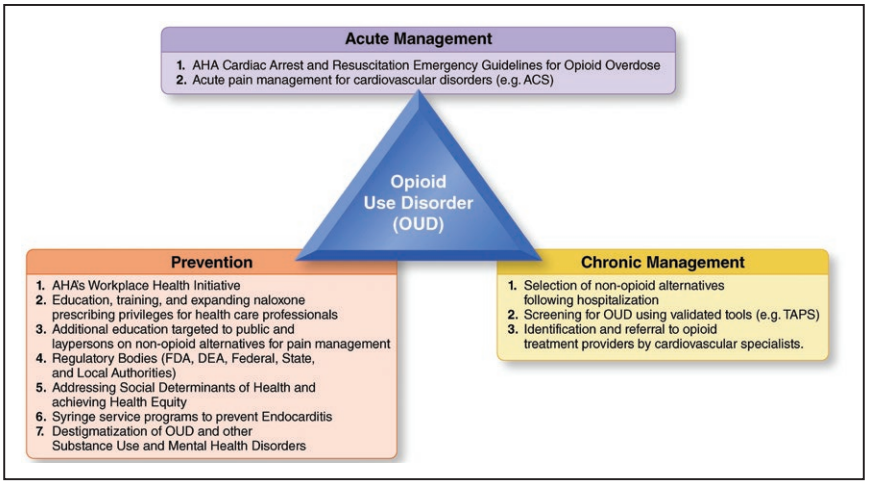

Figure 4. Schematic of opioid use disorder on cardiovascular health and systems of care.
ACS indicates acute coronary syndrome; AHA, American Heart Association; DEA, Drug Enforcement Administration; FDA, Food and Drug Administration; and TAPS, Tobacco, Alcohol, Prescription Medication, and Other Substance Use tool.

Last, as knowledge continues to accrue, implementation research will be critical. Available evidence indicates an enormous gap between what is known about the most basic intervention of medication-assisted therapy and practice,[85] and as more sophisticated knowledge becomes available, research methods aimed at improving adherence to proven effective therapies and health services will be needed. This field will require complex interventions beyond the traditional health care system, as well as community-based interventions and methods such as cluster and stepped wedge randomization.[86]

Gaps in Science Related to Brain Health

The AHA has recently successfully partnered with the Paul G. Allen Frontiers Group to promote fundamental research into the mechanisms of cognitive impairment and brain health. Similar opportunities should be pursued to forge new partnerships on brain research into the neurobiology of opioid exposure and complex behaviors associated with OUD.[87,88] Innovative studies into OUD and pain management research might be envisioned to identify the cognate receptors and signaling cascades at the gene, protein, metabolism, inflammation, and epigenetic pathway levels.[82] Pain circuits targeted for analgesic relief and OUD in the brain are driven by both biological and nonbiological factors. The AHA has understood for some time that social factors influence the incidence, prevalence, treatment, and outcomes of cardiovascular disease.[89] The opioid crisis and resultant addiction, overdoses, and deaths are also influenced by social factors[16] that must be identified and addressed as part of any approach to address this crisis.

Both chronic pain management and opioid addiction are inextricably linked to conditions that underlie the social determinants of health, challenges faced by individuals, caregivers, and families in their respective neighborhoods, urban and rural communities, and the US population at large. OUD affects millions of women (and men) of childbearing age with subsequent consequences for neonatal exposure to opioids and multiple adverse childhood experiences associated with cardiovascular and mental health, stigmatization, and discrimination.[90] Traditional pharmacological approaches in the form of opioid-receptor agonists and antagonists might benefit from research advances of nontraditional options (eg, vaccine and monoclonal antibody administration) by addressing barriers to vaccine development.[91,92] The AHA has a compelling interest in promoting basic, translational, and clinical research into chronic pain and addiction.

Gaps in Research on Brain-Organ Connections

Over the millennia, both philosophers and scientists have opined about the connections and interactions between the mind and the body. Many long-term adverse effects of opioids, which influence addiction, are inextricably linked to certain behavioral patterns in order to avoid certain physiological effects of the withdrawal syndrome. For example, the recently described opioid-induced androgen deficiency is associated with effects of hypogonadism such as reduced libido, depression, and fatigue.[93] Research into the hypothalamic-pituitary-adrenal axis might benefit from recent innovative approaches using optogenetics related to drug abuse and addition.[94] Because recent studies have elegantly mapped the top-down regulation by the brain-spleen connections in adaptive immune responses,[95] it is conceivable that similar fine mapping studies of neural stress centers and putative links to discrete cell surface receptors (ie, adrenergic, acetylcholine) in peripheral organs (eg, lung, heart) may afford new opportunities for drug discovery and improved health outcomes for OUD.

Suggestions/Considerations for Research/Public Health Initiatives

1. The AHA should actively support federal research initiatives such as the impact of genetics and

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societal factors on outcomes and encourage innovations to expand effective treatment options for OUD.

2. Specific comparative-effectiveness trials of care in patients with cardiovascular causes of pain should be conducted.
3. The AHA should consider specific research for the detection and treatment of pain in patients with cardiovascular disease and for basic discovery and translational research to better understand the interaction of cardiovascular biology and the brain with pain to promote translation into new therapies.

CONCLUSIONS

The AHA is committed to addressing the opioid epidemic and advancing the science on opioid use and its effects on patients with cardiovascular disease through evidence-based research; improving education and training for the public and health care professionals on how to safely manage pain, opioid overdose, and support treatment for OUD; and creating and developing partnerships with federal, state, local, and employer-based programs. With these joint efforts and focused partnerships, we anticipate that the death rate of drug overdoses in the United States will decline as we improve health equity and build healthier communities.

ARTICLE INFORMATION

Disclaimer: The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of the National Institute on Drug Abuse, the National Institutes of Health, the US Department of Health and Human Services or the US Department of Veterans Affairs.

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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Elizabeth M. Oliva	VA Program Evaluation and Resource Center	VA Health Services Research and Development investigator-initiated research project (PI on a research grant that began in December 2018 to study the effectiveness of naloxone in preventing opioid overdose among veterans)†	None	None	None	None	None	Department of Veterans Affairs (VA National Opioid Overdose Education and Naloxone Distribution [OEND] coordinator)†

(*Continued*)

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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