



HEALTH RESEARCH AND DEVELOPMENT TO STEM THE OPIOID CRISIS: A NATIONAL ROADMAP

A Report by the

FAST TRACK ACTION COMMITTEE ON HEALTH SCIENCE AND
TECHNOLOGY RESPONSE TO THE OPIOID CRISIS

COMMITTEE ON SCIENCE

of the

NATIONAL SCIENCE & TECHNOLOGY COUNCIL

October 2018

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About the FTAC on Health S&T Response to the Opioid Crisis

In December 2017, OSTP convened a Fast-Track Action Committee (FTAC) on Health Science and Technology (S&T) Response to the Opioid Crisis (Opioid FTAC) under the NSTC Committee on Science. The Opioid FTAC was chartered to facilitate coordination of health research and development (R&D) and related S&T activities across agencies, and with other Administration initiatives, in support of the national response to the opioid crisis; facilitate interagency sharing of opioid-related health R&D findings, standard-based data and tools, and best practices; assess gaps in, and opportunities for strengthening, the R&D and related S&T response to the opioid crisis; and identify opportunities to expedite promising and potentially groundbreaking R&D and public health surveillance efforts to rapidly combat the crisis.

About this Document

This Opioid FTAC Roadmap identifies R&D critical to addressing key gaps in knowledge and tools, and opportunities to improve coordination of Federal R&D essential to combating the opioid crisis. It builds on the recommendations in the report from the President's Commission on Combating Drug Addiction and The Opioid Crisis, as well as recommendations from multiple other sources, including the National Academies report on *Pain Management and the Opioid Epidemic*, the Interagency Pain Research Coordinating Committee's *Federal Pain Research Strategy*, the National Governors Association report on *Governor's Recommendations for Federal Action to End the Nation's Opioid Crisis*, and the Surgeon General's report *Facing Addiction in America*.

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Abbreviations

ASPE	Assistant Secretary for Planning and Evaluation
CDC	Centers for Disease Control and Prevention
DOD	Department of Defense
DOJ	Department of Justice
DOT	Department of Transportation
EMS	Emergency medical services
FTAC	Fast-Track Action Committee
GDP	Gross domestic product
GSA	General Services Administration
HHS	Department of Health and Human Services Human
HIV	immunodeficiency virus
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NSF	National Science Foundation
NSTC	National Science and Technology Council
OASH	Office of the Assistant Secretary for Health
OMB	Office of Management and Budget
ONDCP	Office of National Drug Control Policy
OSTP	Office of Science and Technology Policy
PDMP	Prescription Drug Monitoring Program
R&D	Research and development
SAMHSA	Substance Abuse and Mental Health Services Administration
S&T	science and technology
USDA	Department of Agriculture
VA	Department of Veterans Affairs

Executive Summary

As the opioid crisis continues to devastate the United States and its communities, science and technology have been recognized as key components of the U.S. approach to combat the crisis. Achieving scientific breakthroughs and advancements to help resolve the opioid crisis requires a Federal research portfolio that strategically supports basic, applied, and implementation science. In December 2017, the Office of Science and Technology Policy (OSTP) convened a Fast-Track Action Committee (FTAC) on Health Science and Technology Response to the Opioid Crisis (Opioid FTAC) under the National Science and Technology Council (NSTC) Committee on Science. The Opioid FTAC was charged with creating a Roadmap for health research and development (R&D), and related science and technology (S&T), to support the President's opioid response. This Roadmap achieves its purpose by identifying (1) R&D critical to addressing key gaps in knowledge and tools, and (2) opportunities to improve coordination of R&D essential to combating the opioid crisis.

To organize its efforts and the Roadmap, the Opioid FTAC identified seven areas of R&D: (1) the Biology and Chemistry of Opioid Addiction and Pain; (2) Non-Biological Contributors to Opioid Addiction; (3) Pain Management; (4) Prevention of Opioid Addiction; (5) Treatment of Opioid Addiction and Withdrawal; (6) Overdose Prevention and Recovery; and (7) Community Consequences of Opioid Addiction. The research recommendations generated by the FTAC in each of these areas, as well as an eighth section that includes recommendations on ways to enhance coordination, are summarized below.

Biology and Chemistry of Pain and Opioid Addiction

- Elucidate the mechanisms and pathways that underlie both opioid addiction and pain.
- Integrate various investigative approaches to better understand the full complexity of opioid addiction and pain.
- Develop novel models, methods, and tools to study the basic biology of opioid addiction and pain.

Non-Biological Contributors to Opioid Addiction

- Characterize and develop effective approaches to address stigma.
- Identify the sociocultural and socioeconomic factors that contribute to opioid misuse and addiction to inform effective risk mitigation strategies.
- Increase understanding of how geographic disparities influence the effectiveness of prevention and treatment approaches.
- Investigate how gaps in public and professional knowledge contribute to opioid misuse in patients.
- Study the efficacy of policies designed to address the opioid crisis.
- Investigate the impact of clinical and coverage policies on pain management, opioid misuse, and addiction.

Pain Management

- Understand the factors driving the transition from acute to chronic pain.
- Develop non-addictive alternatives to opioids for treatment of acute and chronic pain.
- Determine effective, evidence-based, non-opioid, and non-pharmacological therapies and interventions for pain management.
- Develop and test models and clinical practice guidelines for integrated pain management.
- Study the risks and benefits of treating and managing childhood and adolescent pain with opioids and develop and test alternative strategies.
- Develop advanced, objective tools to more accurately, reliably, and quantitatively assess pain.

Prevention of Opioid Addiction

- Improve data collection and interoperability to track and assess the opioid crisis and response.
- Assess ways opioid marketing, packaging, and disposal are related to opioid misuse and inappropriate access to prescription opioids.
- Test whether the long-term impact of early childhood and adolescent interventions reduce later opioid misuse and use disorder.
- Determine the effectiveness of population-based interventions, such as national, multi-platform media and awareness campaigns, to reduce demand for prescription and illicit opioids.
- Evaluate the effectiveness of clinical interventions to reduce unnecessary use and misuse of prescription opioids.
- Identify strategies to improve real-time or near real-time use of interoperable and interconnected databases and access to data—including prescription drug monitoring program data—to curb overprescribing and misuse of opioids.
- Determine how to scale up and sustain preventive strategies locally.

Treatment of Opioid Addiction and Withdrawal

- Determine the effectiveness of novel approaches in treating opioid addiction, including new medications, vaccines, and devices as part of treatment.
- Conduct research to inform development of best practices and guidelines for opioid addiction treatment in women who are or plan to become pregnant that considers risks and benefits to both the pregnant woman and the developing fetus.
- Develop smart technologies to deliver care, support recovery, and monitor the impacts of pharmacological therapeutics.
- Conduct research to inform the development and effective implementation of clinical best practices, guidelines, and standards for the treatment of opioid addiction.
- Enhance access to care through innovative strategies.
- Assess the effectiveness of peer and faith-based recovery support services as a component of the public health response.
- Determine how to integrate public health approaches into criminal justice settings.

Overdose Prevention and Recovery

- Develop additional methods for preventing opioid overdose deaths, such as vaccines, devices, and novel medications.
- Develop new tools and local capacity to detect, identify, and characterize novel synthetic opioids.
- Research communication strategies to enhance awareness of opioid overdose reversal medication in at-risk populations and clinical service providers.
- Identify and track trends in fatal and non-fatal opioid overdoses to inform distribution and availability of appropriate products and services.
- Research appropriate access to, and delivery of, overdose reversal products and services.
- Conduct research to identify factors associated with successful and unsuccessful long-term outcomes for people who have overdosed.

Community Consequences of Opioid Addiction

- More quickly and accurately assess opioid morbidity and mortality.
- Identify how public health resources can be effectively allocated with the goal of long-term sustainability.

- Identify how existing public health system actions, services, and partnerships can be leveraged to build resilience in communities impacted by the opioid crisis.
- Determine the efficacy of innovative and creative approaches to the opioid response that address a community's unique features and culture.
- Monitor the full impact of prenatal opioid exposure on infant health and child development.
- Examine the vulnerabilities of children residing with opioid-addicted caregivers, including developmental delays and addiction trajectory.
- Evaluate the role of recovery community organizations in mitigating community consequences of opioids, including faith-based recovery communities.
- Determine the fate and transport of opioid and opioid metabolites in the environment.

Opportunities for Enhanced Coordination

- Align related research funding opportunity announcements.
- Establish a Federal opioid crisis research community of practice.
- Promote additional coordination of the public health community with law enforcement and other justice systems working to address the opioid crisis.

These research recommendations are intended to serve as a guide that identifies opportunities for strengthening, expanding, and further coordinating core research and development efforts to reduce the adverse public health impact of opioids and maximize the public health benefit of Federal investments.

Introduction

Opioid misuse, addiction, and overdose have reached crisis levels in the United States. In addition to the misuse and abuse of prescription opioids, a dynamic illicit drug market is causing an increasing number of deaths due to overdose, including deaths from novel compounds previously unknown to the scientific community. From 1999 to 2016, the number of overdose deaths involving opioids increased more than five-fold, from 8,050 deaths to 42,250 (Figure 1).¹ Both prescription and illicit opioids (e.g., heroin) contributed to this increase, with deaths involving synthetic opioids spiking in the most recent years, from 3,100 deaths in 2013 to over 19,400 in 2016.² Prescription opioids have been the mainstay of pain management for many of the 100 million adults with chronic pain.³ Safer treatment options are needed to reduce our reliance on opioids for pain relief.

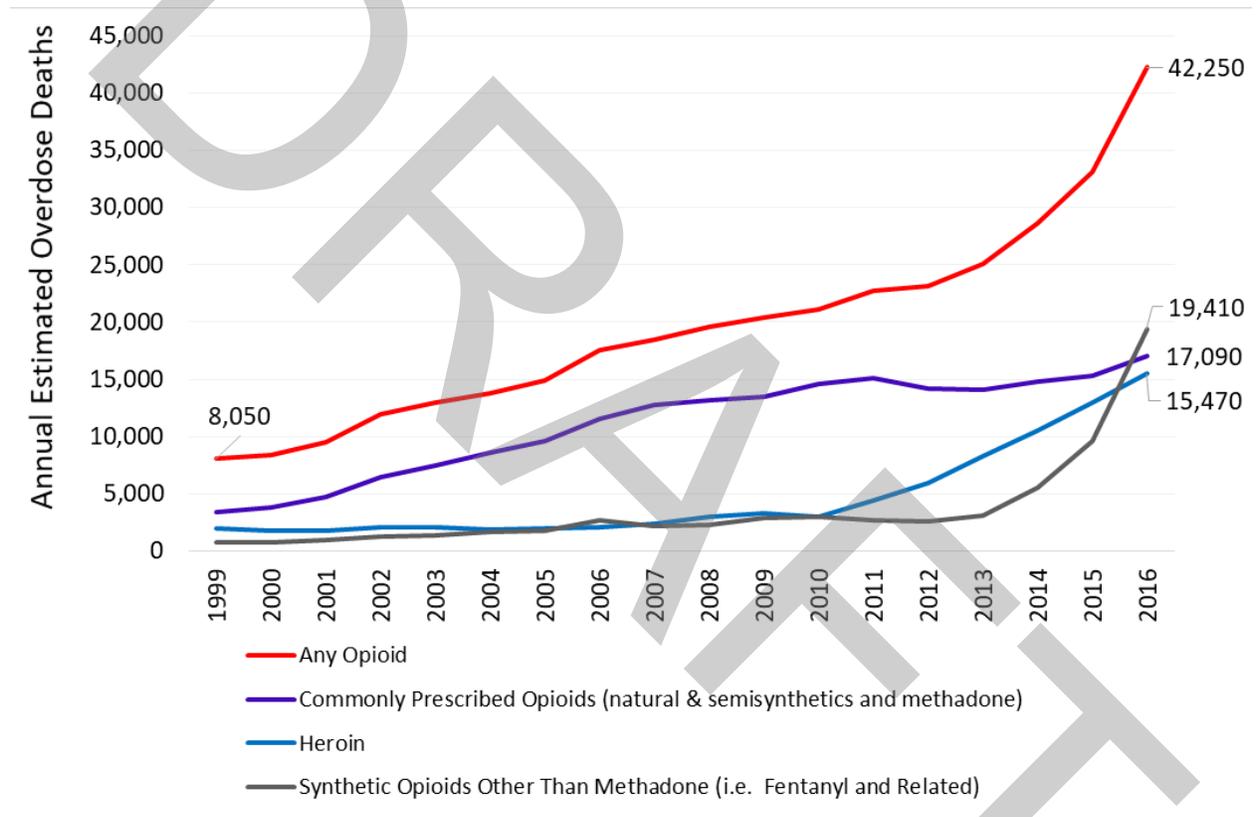


Figure 1: Drug Overdose Deaths in the U.S. Involving Opioids, 1999 to 2016. Source: NCHS WONDER, National Vital Statistics System, Mortality

¹ <https://www.cdc.gov/nchs/data/databriefs/db294.pdf>

² <https://www.ncbi.nlm.nih.gov/pubmed/29715347>

³ <https://www.ncbi.nlm.nih.gov/pubmed/22553896>

Other consequences of the opioid crisis include high rates of opioid addiction and,⁴ increasing infectious disease transmission (such as Hepatitis, HIV, and bacterial infection) due to sharing of injection paraphernalia, including needles.^{5,6} The impacts of the opioid crisis are not limited to users themselves, but extend to their families and their communities. For example, in the United States in 2014, one infant is born every 15 minutes diagnosed with opioid withdrawal after being exposed to opioids before birth; the rate of neonatal opioid abstinence syndrome has increased by 433% (1.5 to 8.0 per 1000 hospital births) from 2004 to 2014.^{7,8} A recent multi-state analysis of opioid use disorder among delivery hospitalizations reported that from 1999–2014, the national prevalence of opioid use disorder increased 333%, from 1.5 cases per 1,000 delivery hospitalizations to 6.5, an average annual increase of 0.4 per 1,000 delivery hospitalizations per year.⁹ These direct and indirect consequences of the opioid crisis carry a substantial economic cost, estimated at \$504 billion in 2015—2.8 percent of GDP—according to the White House Council of Economic Advisers.¹⁰

The Trump Administration has taken decisive steps to combat the opioid crisis. In March 2017, President Trump established the President’s Commission on Combating Drug Addiction and the Opioid Crisis.¹¹ In October 2017, the President directed the Department of Health and Human Services (HHS) to consider whether to declare the opioid crisis a nationwide public health emergency.¹² In March 2018, the White House announced the President’s Initiative to Stop Opioid Abuse and Reduce Drug Supply and Demand, which identifies research and development (R&D) as an integral component of the comprehensive response to the crisis.¹³

Achieving scientific breakthroughs and advancements to help resolve the opioid crisis requires a federal research portfolio that strategically supports basic, applied, and implementation research. The FTAC Report builds on the recommendations in the President’s Commission on Combating Drug Addiction and The Opioid Crisis’ report¹⁴ as well as recommendations from multiple other sources, such as the National Academies’ report on *Pain Management and the Opioid Epidemic*,¹⁵ the Interagency Pain Research Coordinating Committee’s *Federal Pain Research Strategy*,¹⁶ the National Governors Association’s report on *Governor’s Recommendations for Federal Action to End the Nation’s Opioid*

⁴ <https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf>

⁵ <https://www.ncbi.nlm.nih.gov/pubmed/27468059>

⁶ <https://www.ncbi.nlm.nih.gov/pubmed/25950251>

⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520760/>

⁸ <https://www.ncbi.nlm.nih.gov/pubmed/29572288>

⁹ <http://dx.doi.org/10.15585/mmwr.mm6731a1>

¹⁰ <https://www.whitehouse.gov/briefings-statements/cea-report-underestimated-cost-opioid-crisis/>

¹¹ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

¹² <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>

¹³ <https://www.whitehouse.gov/briefings-statements/president-donald-j-trumps-initiative-stop-opioid-abuse-reduce-drug-supply-demand-2/>

¹⁴ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

¹⁵ <https://www.nap.edu/catalog/24781/pain-management-and-the-opioid-epidemic-balancing-societal-and-individual>

¹⁶ <https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview>

Crisis,¹⁷ and the previous Surgeon General's report *Facing Addiction in America*,¹⁸ among others. The complexity of this evolving crisis requires new discoveries and improvements to existing approaches across a broad spectrum of topics—from the biology of addiction to overdose prevention. Therefore, the Opioid FTAC's scope included a broad range of health-related R&D with relevance to the opioid crisis, including basic and clinical research on pain and addiction; development and optimization of treatments for pain, opioid-use disorder (OUD), and opioid overdose; studies that examine the causes of and risk factors for opioid misuse, addiction, and overdose; implementation research to determine optimal strategies for fielding proven interventions; and research on the effectiveness of information and communication technologies in supporting OUD treatment and overdose prevention and care.

With this scope in mind, the FTAC consulted scientific literature and previous reports, conducted a survey of Federal departments and agencies, and leveraged its members' subject matter expertise to develop this Roadmap. It devotes one chapter to each of seven general areas of R&D: (1) the Biology and Chemistry of Pain and Opioid Addiction; (2) Non-Biological Contributors to Opioid Addiction; (3) Pain Management; (4) Prevention of Opioid Addiction; (5) Treatment of Opioid Addiction and Withdrawal; (6) Overdose Prevention and Recovery; and (7) Community Consequences of Opioid Addiction. Each chapter includes a statement of the long-term desired goal for R&D in the area; a review of the current state of science; and discussion of gaps and R&D needs. Chapter 8 identifies cross-cutting needs relevant to more than one R&D topic and discusses opportunities for enhanced coordination.

1. Biology and Chemistry of Pain and Opioid Addiction

Goal Statement

Combating the opioid crisis requires an improved understanding of the biological and chemical aspects of opioid use and addiction and pain. One important component of that research is the study of mechanisms acute and chronic pain to help identify non-opioid treatment targets. Research in this area aims to elucidate physiological mechanisms of both addiction and pain, identify biomarkers of vulnerability and resilience, and find potential treatment targets. Additionally, due to the number of overdose deaths from novel compounds and other illicit opioids, the biology and chemistry of synthetic opioids need to be examined to inform the development of new technologies and standards to detect these novel compounds.

State of the Science

Opioids are molecules that interact with opioid receptors in brain cells and other parts of the body, such as the intestinal tract. Much of the recent research on the biology and chemistry of opioid addiction and pain has focused on understanding the underlying mechanisms of these interactions. For instance, recent studies have improved understanding of the structure of opioid receptors and downstream cellular signaling.^{21,22} In addition, genetic research on ion channels in patients with inherited pain

¹⁷ <https://www.nga.org/letters-nga/opioid-crisis-legislation/>

¹⁸ <https://addiction.surgeongeneral.gov/sites/default/files/surgeon-generals-report.pdf>

¹⁹ <https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview>

²⁰ <https://www.nga.org/letters-nga/opioid-crisis-legislation/>

²¹ <https://www.ncbi.nlm.nih.gov/pubmed/28125215>

²² <https://www.ncbi.nlm.nih.gov/pubmed/24460711>

conditions has established the role of these channels in pain sensation,²³ suggesting potential new approaches to treating pain without use of opioids. Researchers have also used neurochemical approaches to study opioid receptors and their relationship to physiological parameters, leading to one of the fundamental insights in the field: an understanding of the overlap between the pain and reward systems and addiction.²⁴⁻²⁶ Other research has examined the biology and chemistry of vulnerability and resilience to addiction, pain, and risk-taking behavior.²⁷

Research Gaps and Needs

While there is a substantial body of research on the basic biology and chemistry of opioid addiction and pain, much of that work has been conducted in isolation. To propel the field forward, it is critical that studies integrate these approaches and their results to characterize the multidimensional nature of these conditions. Similarly, there is a need for new tools that enable investigations with greater spatial and temporal resolution, as well as under more realistic conditions. This will allow for the full complexity of human biology to be understood, and enable improved chemical compound detection and characterization.

- **Elucidate the mechanisms and pathways that underlie both opioid addiction and pain.** There is a need to understand the chemical and biological mechanisms that underlie pain perception, cause the shift from therapeutic use of opioids to addiction, enable abstinence, and contribute to relapse. This research would advance the understanding of molecular aspects of selective receptor binding, neurochemical pathways, intracellular signaling, and relevant cellular interactions. The work should examine how opioids produce chemical and biological changes in the brain and how those physiological changes translate into behavioral changes. It is also important to understand how opioids influence the immune response and increase vulnerability to infections, which amplifies the harmful consequences of addiction on human health.
- **Integrate various investigative approaches to better understand the full complexity of opioid addiction and pain.** Methodologies and investigative approaches are often used in isolation, and, in many cases, the relationships among the results are poorly understood. There is a need for studies that combine approaches to improve understanding of the complex physiological aspects of addiction and pain. For example, imaging, genetic, and biobehavioral data, can all be used to understand susceptibility and resilience on an individualized basis. This integration can lead to a better understanding of how the insights gained from each study correspond to one another and impact pain avoidance, drug-seeking, and addiction relapse behaviors.
- **Develop novel models, methods, and tools to study the basic biology of opioid addiction and pain.** There are numerous models to approximate and study addiction and pain in controlled, experimental settings. However, there is no consensus on how these generalized models can be applied to assess and treat individuals. Studies are needed to assess the utility and limitations of each model, develop standards, and better characterize how variables measured in models correspond to the relevant condition. Where models fail to sufficiently

²³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2096434/>

²⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28778406>

²⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28501595>

²⁶ <https://www.ncbi.nlm.nih.gov/pubmed/27872581>

²⁷ <https://www.ncbi.nlm.nih.gov/pubmed/27339423>

approximate the human condition, new tools should be developed, such as smart pills and biosensors, to enable the study of opioid addiction and pain directly in individual patients.

2. Non-Biological Contributors to Opioid Addiction

Goal Statement

The non-biological contributors to opioid addiction include psychosocial, environmental, geographic, socioeconomic, and educational domains. The goal of research in these areas is to better understand how these factors contribute to opioid addiction, in isolation and through interaction with each other and with biological factors.

State of the Science

Research on the non-biological contributors to opioid addiction has examined the influence of various factors on vulnerability to addiction. One prominent approach has focused on contributors to opioid addiction at the level of the individual, while another arm of research has examined how community-level and policy-level factors have contributed to the opioid crisis. Research indicates that an individual's employment status, socioeconomic status, access to education and healthcare, mental health, home environment, race, culture, adverse childhood experiences (ACEs), and exposure to discrimination influence susceptibility to opioid addiction.²⁸ Other factors under examination include medical and pharmaceutical company history and practices, geographic and socioeconomic variation, and the stigma of drug abuse and addiction.²⁹⁻³²

Of note, many individuals with addiction and/or mental disorders have experienced a significant level of trauma and/or ACEs. For example, a 2016 study demonstrated a clear dose response relationship between the number of traumatic experiences and increased risk of prescription drug misuse in adults. Individuals who reported five or more ACEs were three times more likely to misuse prescription pain medication and five times more likely to engage in injection drug use. Another study found that over 80% of the patients seeking treatment for opioid addiction had at least one form of childhood trauma, with almost two-thirds reporting having witnessed violence in childhood. Among the different forms of ACEs, sexual abuse and parental separation (for women) and physical and emotional abuse (for men) appear to be particularly highly correlated with opioid abuse. In one study, although childhood trauma alone did not predispose the development of opioid addiction, individuals with high childhood trauma scores were more likely to display antisocial behavior and to have complicated addiction histories.³³

Research Gaps and Needs

While research has identified a number of non-biological variables that impact susceptibility to addiction, additional studies are needed to (1) further elucidate the underlying mechanisms, (2) understand how such factors interact with one another and with biological factors to produce their

²⁸ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913691/>

²⁹ <https://www.ncbi.nlm.nih.gov/pubmed/11467250>

³⁰ <https://hbr.org/2017/10/to-combat-the-opioid-epidemic-we-must-be-honest-about-all-its-causes>

³¹ <https://www.ncbi.nlm.nih.gov/pubmed/29267060>

³² <https://www.brookings.edu/research/un-burying-the-lead-public-health-tools-are-the-key-to-beating-the-opioid-epidemic/>

³³ https://publichealth.gwu.edu/sites/default/files/downloads/Redstone-Center/CTIPP_OPB_final.pdf

effects on addiction vulnerability, and (3) evaluate how policies and programs related to these factors mitigate or compound their influence. Specific research needs are highlighted below:

- **Characterize and develop effective approaches to address stigma.** Stigma acts to discourage individuals from seeking treatment due to social isolation, depression, and anxiety. There is a need to investigate the cultural, educational, and geographic context of stigma and its impact on opioid misuse, addiction vulnerability, and access to, and utilization of, addiction treatment. Research is also needed to understand the effects of stigmatization on employment, interpersonal relationships, self-worth, and access to mental healthcare, which in turn affect opioid addiction and treatment outcomes.
- **Identify the sociocultural and socioeconomic factors that contribute to opioid misuse and addiction to inform effective risk mitigation strategies.** Research into the linkages between opioid misuse and socioeconomic factors would help identify causes of and possible mitigating interventions for high rates of opioid misuse and addiction observed in some populations. These insights may shed light on the relationships and pathways between opioid misuse, alcohol and tobacco misuse, and the use of other illicit drugs. Factors that should be further investigated in terms of association, causality, and potential for preventive intervention include poverty, unemployment, underemployment, work history, race and ethnicity, gender, mental health, health insurance coverage, homelessness, family history, and geographic and social isolation.
- **Increase understanding of how geographic disparities influence the effectiveness of prevention and treatment approaches.** Research should investigate how local context influences the effectiveness of different prevention interventions and public health strategies. Furthermore, for those regions where traditional prevention and treatment approaches are inaccessible, research should explore how technology can be used to develop locally appropriate solutions.
- **Investigate how gaps in public and professional knowledge contribute to opioid misuse in patients.** Additional research is needed to understand the gaps in provider, pharmacist, and user knowledge and behavior that may be inhibiting public awareness of the addictiveness of opioids and implementation of proper prescribing practices by healthcare professionals.
- **Study the efficacy of policies designed to address the opioid crisis.** The political and regulatory environment affects the opioid crisis in many ways, including influencing stigmatization, resource availability, and access to care. Federal, State, local, territorial, and Tribal policies related to mitigating rates of overdose, providing addiction treatment, improving and sustaining surveillance systems, and preventing opioid misuse all impact opioid addiction and overdose rates. Research is needed to relate program practices to outcomes to better guide policymakers in addressing the opioid crisis.
- **Investigate the impact of clinical and insurance policies on pain management, opioid misuse, and addiction.** Understanding the complex interactions of financing, clinician practices, and patient behaviors will take both basic descriptive research as well as experimental studies to test theories that may explain behaviors. To inform the development of novel interventions, studies are needed to examine the direct and indirect effects of clinical and coverage policies on pain management (including interdisciplinary and non-opioid pain management), opioid misuse, and addiction.

3. Pain Management

Goal Statement

While opioids can be effective in managing pain, the current opioid crisis has drawn attention to the importance of limiting opioid exposure in the treatment of acute and chronic pain. Advances in pain management research make it possible to achieve the goal of a functional life with integrative pain management while curbing opioid exposure. Improvements in the clinical understanding of pain management have resulted in enhanced treatment protocols and prevention approaches for acute and chronic pain, thereby improving productivity, quality, and length of life while mitigating risk of opioid misuse. Expanding viable multimodal and multidisciplinary treatment options, including developing adjuncts and alternatives to opioids, is critical to limiting opioid exposure and reducing the supply available for non-medical opioid use.

State of the Science

Pain is an unpleasant physical and/or emotional experience that manifests as multiple, complex conditions—not a single phenomenon experienced in a singular manner.³⁴ According to an analysis funded by the National Institutes of Health, approximately 25 million American adults suffer from chronic pain that is present daily.³⁵ Multiple clinical guidelines exist for managing pain. CDC’s Guideline for Prescribing Opioids for Chronic Pain helps increase provider’s ability to offer safer, more effective pain management.³⁶ This guideline addresses initiation of opioid use for chronic pain, and recommends alternatives such as non-opioid medications, non-pharmacologic treatments for pain, and integration with behavioral and mental health. Other guidelines emphasize holistic approaches that include individualized, patient-centered care and use a broad range of interventions, including psychological treatment, as indicated.^{37,38} One focus of current efforts to enhance these guidelines examines the diversity of pain therapies, including pharmacological/non-pharmacological combinations and other strategies that are tailored to individuals and specific populations. In addition, research and development activities in pain management across the Federal Government address a variety of topics, including standardized measures of pain and pain registries, initial dosing for acute pain, and precision medicine strategies tailored to individuals and specific populations including pregnant women.³⁹

Research Gaps and Needs

Research and development in acute and chronic pain treatment—including pharmacological, non-pharmacological, interventional, and multimodal pain management—is essential to relieve the burden of pain and mitigate the use of prescription opioids. Emerging treatments include non-addictive analgesics and non-pharmacologic approaches, such as cognitive behavioral therapy, as well as multimodal and multidisciplinary therapies. Beyond the effectiveness of non-pharmacological approaches, it is also important to examine their access and availability to patients.⁴⁰ Strengthening

³⁴ <https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698&navItemNumber=576#Pain>

³⁵ <https://www.ncbi.nlm.nih.gov/pubmed/26028573>

³⁶ <https://www.ncbi.nlm.nih.gov/pubmed/26987082>

³⁷ <https://www.ncbi.nlm.nih.gov/pubmed/22786449>

³⁸ <https://www.ncbi.nlm.nih.gov/pubmed/22227789>

³⁹ <https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview>

⁴⁰ <https://www.ncbi.nlm.nih.gov/pubmed/26987082>

the evidence-base for these treatment approaches will enhance treatment options and provide patients with safer, more efficacious pain treatments. Furthermore, in order to make pain treatment more accessible and patient-centered, it is necessary to incorporate patient perspectives on delivery of individualized pain treatments (e.g. pharmacogenomics) and examine the relationship of pain to social, economic, and community conditions. Research should consider age groups and populations that have special needs that may need to be addressed (e.g., infants with prenatal exposure, children, pregnant and breast-feeding women, and older adults). These research activities can contribute to improving the evidentiary base for effective acute and chronic pain treatment guidelines.

- **Understand the factors driving the transition from acute to chronic pain.** The cognitive and neural processes related to risk or resilience of transitioning from acute to chronic pain need to be explored. By elucidating neural processes, advancements can be used to better treat acute pain and thereby mitigate or prevent chronic pain, reducing the need for sustained opioid-based pain treatment. Collaborative research and data networks can play a role in establishing multi-institutional and multi-sector collaborations to focus on clarifying the basic mechanisms that lead to chronic pain.
- **Develop non-addictive alternatives to opioids for treatment of acute and chronic pain.** There is a need to develop pharmacological and non-pharmacological pain treatments without euphoric and addictive effects, including innovative devices to treat pain without medications. Prioritizing research and development of non-addictive pain treatments through public-private partnerships with private sector pharmaceutical partners is critical to addressing these needs.
- **Determine effective, evidence-based, non-opioid, and non-pharmacological therapies for pain management.** While some alternative therapeutics are available, evidence-based studies that inform health care coverage are needed. Complementary and integrative health care approaches may be useful for developing personalized treatments. For example, acupuncture, yoga, exercise, diet, and physiological, and mindfulness therapies should be assessed in the treatment of chronic pain, especially when the pain presents with co-morbid conditions such as fatigue, anxiety, and post-traumatic stress disorder (PTSD).
- **Develop and test models of care and clinical practice guidelines for integrated pain management.** Developing better models of integrated pain management requires multidisciplinary teams of physicians and providers. Better pain management requires clinical guidelines that empower patients and physicians to work together to develop optimal treatment plans. Research is needed to better elucidate which treatment options are indicated in the course of a pain condition. Enhancing the delivery of multidisciplinary approaches is vitally important.
- **Study the risks and benefits of treating and managing childhood and adolescent pain with opioids and develop and test alternative strategies.** It is important to better understand pain management in children and youth to help prevent the development of chronic pain into adulthood. It is also important to understand the risks associated with opioid use for children, including risks for opioid addiction in adulthood. Research on evaluating risks and benefits of opioid use in children and adolescents should focus on culturally appropriate health measures for screening, service and delivery, and promoting physical and psychosocial well-being.
- **Develop tools for accurate assessment of pain.** Clinical and research assessment of pain in humans is largely based on self-report and limited measures that constrain the ability to make

progress in pain-related research. Research is needed to develop new tools for the objective assessment of pain, such as the use of biomarkers for personalized treatment interventions.

4. Prevention of Opioid Addiction

Goal Statement

The overarching long-term goal in combating the opioid crisis is the prevention of opioid misuse and addiction, while delivering effective pain management. This will be accomplished through research and coordinated implementation of interventions, policies, public health efforts, and clinical strategies to: (1) provide primary prevention services (e.g., strengthening protective factors, especially for infants, youth, and those with risk factors that potentiate misuse); (2) improve appropriate prescribing practices of opioids and expand non-opioid approaches to pain care; and (3) accelerate research to facilitate early intervention when misuse is identified.

State of the Science

To aid in the prevention of opioid addiction, current research efforts focus on how to reduce the supply and demand for opioids. From a supply reduction perspective, ongoing health research and development focused on efforts to reduce availability of opioids investigates: policy, regulatory, and health systems approaches to opioid prescribing practices;⁴¹ labelling authority, prescribing guidelines (e.g., CDC Guideline⁴²), and Medicare and Medicaid drug utilization review programs; as well as changes to the standard of care and care delivery strategies including complementary, alternative, and integrative treatments for pain.^{43,44}

Ongoing research and development focused on optimizing demand reduction efforts includes: public health and faith and community-based prevention approaches (e.g., public health campaign, media, marketing and messaging strategies); strategies that reduce the introduction of opioids into adolescent and young adult populations; new pain medication modes of action and delivery; and identification of opioid use disorder (secondary prevention) and linkage to treatment (tertiary prevention).

Research Gaps and Needs

The key gaps in prevention include improving availability of and access to non-opioid therapies for pain and assessing the efficacy of potential interventions that have not yet been proven effective (e.g., drug disposal programs and media campaigns). These data are needed to accelerate and better target interventions to reduce supply and demand for prescription and illicit opioids. Knowledge gaps also exist in how to tailor interventions demonstrated effective in one setting for implementation in another (e.g., rural versus urban settings, academic health systems versus small group practices, pregnant versus non-pregnant populations). In addition, improved, timely, and coordinated data on outcomes such as opioid use disorder and neonatal abstinence syndrome are needed in order to measure effects of interventions as well as overall progress in preventing opioid addiction. Finally, better information can help target community interventions to local needs based on community epidemiology and target individualized interventions based on individual and contextual factors and needs.

⁴¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994311/>

⁴² <https://www.ncbi.nlm.nih.gov/pubmed/26987082>

⁴³ <https://www.ncbi.nlm.nih.gov/pubmed/27400353>

⁴⁴ <https://www.ncbi.nlm.nih.gov/pubmed/29340937>

- **Improve data collection capabilities and data interoperability for epidemiological tracking and assessment of the opioid crisis and response.** Expansion of public health surveillance and laboratory data, first responder and law enforcement data, and information sharing capabilities are needed to inform and aid in public health, public safety, and clinical decision-making in response to the opioid crisis. Timely and coordinated data collection on drug supply, epidemiology, and outcomes (e.g., incidence of prescription opioid use, heroin use, illicit synthetic opioid use, naloxone administration, neonatal abstinence syndrome) is necessary to track the opioid crisis and evaluate the impact of specific interventions. Additionally, data standardization and interoperability is critical to advance these efforts. Convergent research combining operations research, data science, and behavioral and economic sciences is essential.
- **Assess ways opioid marketing, packaging, and disposal are related to opioid misuse and inappropriate access to prescription opioids.** Marketing, packaging, and disposal strategies could play an important role in discouraging prescription opioid misuse and limiting supply to the secondary market. Research should identify effective approaches to encourage appropriate opioid use, storage, and disposal practices. For example, prescription drug disposal and take-back programs have been explored; however, there is insufficient data to determine outcomes of such strategies. Conversely, illicitly supplied, counterfeit medications and synthetic opioids are highly advertised and accessible via internet, including the “dark web.” Research into strategies to understand and dismantle the dark web marketplace for direct-to-consumer purchases of counterfeit medications and synthetic opioids is critical.
- **Test whether the long-term impact of early childhood and adolescent interventions reduce later opioid misuse and use disorder.** Opioid misuse and opioid use disorder have been associated with risk factors such as other substance use and mental health disorders. While some research supports a role for early childhood and adolescent primary prevention as a way to reduce the onset of opioid misuse,⁴⁵ additional work is needed to determine its impact on modifiable risk and protective factors.⁴⁶ This includes research on the impact of early childhood and adolescent mental health services and other social services on opioid misuse. Additional research is needed to understand the impact of prenatal opioid exposure on children’s health and development.
- **Determine the effectiveness of population-based interventions to reduce demand for prescription and illicit opioids.** Strategies across the prevention spectrum have the potential to reduce demand for prescription and illicit opioids. These interventions include effective public health messaging, multi-platform media campaigns, community, congregational, and school-based prevention programs, early identification of opioid use disorder, and successful linkage to effective treatment. Research is needed to understand how to tailor these strategies to the specific needs of each community in order to scale the effectiveness of each intervention.
- **Evaluate the effectiveness of clinical interventions to reduce unnecessary use and misuse of prescription opioids.** It is important to understand which interventions are most effective in changing clinical practice and opioid prescribing in order to reduce unnecessary use and misuse of prescription opioids. Screening for opioid misuse during routine medical and obstetric visits could also be considered. At the same time, it is also important not to over-restrict the use of

⁴⁵ <https://www.ncbi.nlm.nih.gov/pubmed/23409883>

⁴⁶ <https://www.ncbi.nlm.nih.gov/pubmed/29169767>

opioids in the appropriate management of pain through precipitous tapering in patients who are otherwise stable, or to avoid prescribing opioids altogether. This topic might also include related research on the effects of national and state level prescribing policies on opioid misuse, related morbidity and mortality rates, and potential harms to patients by inappropriate restrictions on opioids access.

- **Identify strategies to improve real-time or near real-time use of interconnected databases and access to data—including PDMP data—to curb overprescribing and misuse of opioids.** Prescription drug monitoring programs (PDMPs) increase the ability of physicians, pharmacists, and hospitals to evaluate patients' complete prescription and use profiles and help identify patients who may be seeking opioid prescriptions from multiple providers. Research is needed to streamline and standardize PDMP data formats and inputs to maximize public health benefits. Allowing health data to seamlessly follow the patient across data systems (e.g. PDMP, electronic health records, first responder databases) may help ensure clinicians can provide appropriate care for patients who have overdosed. Machine learning is one potential tool that could be leveraged to achieve these goals by helping to identify patterns and relationships between prescribing practices and prescription opioid misuse. Additional surveillance systems that collect data on pregnant women and their infants can identify children born with neonatal abstinence syndrome and other adverse birth outcomes (e.g., birth defects) and can link children and families to services to improve childhood outcomes and referral and/or retention in addiction treatment programs.
- **Determine how to scale up and sustain preventive strategies locally.** Different combinations of strategies may be needed in different areas based on dynamic geographic differences in burden of prescription versus illicit opioids and disparities in available resources. Better evidence on what works in various regions will help tailor and target preventive state, local, Tribal, and territorial interventions more effectively.

5. Treatment of Opioid Addiction and Withdrawal

Goal Statement

The ultimate goal of treatment of opioid addiction and withdrawal, including neonatal opioid abstinence syndrome, is to prevent the serious health and social harms associated with opioid misuse. Achieving this objective requires research to develop more effective and novel therapies and to identify effective and efficient ways to implement current evidence-based treatments, including both medication-assisted treatments (methadone, buprenorphine, and naltrexone) and ancillary psychosocial supports. The patient perspective is essential in guiding the development of treatment options.

State of the Science

Many aspects of opioid addiction treatment have been researched, including underlying addiction pathways in the brain, pharmacotherapies with and without psychosocial support, and behavioral therapies to treat opioid addiction while managing symptoms of withdrawal and abstinence. For example, use of medication-assisted treatments, such as methadone, buprenorphine and extended-

release naltrexone, have been shown to be effective in retention and suppression of illicit opioid use.⁴⁷⁻
⁴⁹ Nevertheless, treatment plans should be individualized for a patient’s unique needs and preferences; there is no “one size fits all” approach.

Pregnant women, embryos, and fetuses are especially vulnerable to the effects of opioid misuse. Opioid exposure during pregnancy carries significant risks for the unborn baby, including stunted growth, preterm labor, fetal convulsions, fetal death, and neonatal opioid withdrawal syndrome. There has been an estimated five-fold increase in the number of babies born with neonatal opioid withdrawal in the United States between 2000 and 2012, and it was estimated that a baby is born suffering and diagnosed with opioid withdrawal every 15 minutes in 2014.^{50,51}

Research on treatment practices has also demonstrated that short-term treatment of withdrawal without continued care is ineffective and puts individuals with opioid addiction at high risk for relapse and overdose death.⁵² At the state level, introduction of treatment programs in criminal justice settings that include a linkage to medication and continued support after release has been shown to be a promising strategy.^{53,54} Regardless of the specific treatment modality employed, engagement with provider and psychosocial support is critical to the success of opioid addiction treatment.

Research Gaps and Needs

Research on treatment of opioid addiction has often been constrained to short-term studies with limited generalizability, presenting challenges with translating research findings into practice, especially to rural settings and to individuals with co-occurring mental and/or physical conditions. Research on treatment modalities should investigate the needs of vulnerable populations and those with complex needs, such as pregnant and post-partum women. Individualized or personalized care that considers pharmacogenomics, is also an area for further exploration. In addition, there has been limited research on how to implement opioid addiction treatment in non-specialty care settings and on emerging service delivery models. These research priorities are critical to the advancement of opioid addiction treatment. Both surveillance and research have strengths and weaknesses, but together they will provide a clear picture of how we can best address the needs of pregnant women with opioid use disorder and their infants. Observational data from surveillance allows us to monitor trends over time, including the types of opioid and other exposures that may affect medication-assisted treatment (MAT) retention and pregnancy outcomes. Research in a controlled setting can test some hypotheses observed in surveillance data and can test which associations may be causal.

- **Determine the effectiveness of novel approaches in treating opioid addiction, including new medications, vaccines, and devices as part of treatment.** Expansion of the treatment arsenal for opioid addiction is essential to effectively treat opioid addiction. The portfolio of treatment

⁴⁷ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

⁴⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27776678>

⁴⁹ <https://www.ncbi.nlm.nih.gov/pubmed/25822268>

⁵⁰ <https://www.ncbi.nlm.nih.gov/pubmed/22525931>

⁵¹ <https://www.ncbi.nlm.nih.gov/pubmed/9547764>

⁵² <https://www.ncbi.nlm.nih.gov/pubmed/26406300>

⁵³ <https://www.ncbi.nlm.nih.gov/pubmed/29450443>

⁵⁴ <https://www.drugabuse.gov/publications/principles-drug-abuse-treatment-criminal-justice-populations/principles>

options must include both pharmacologic and non-pharmacologic treatments, such as medication, behavioral therapy, and psychosocial support. Research is needed to catalogue current practices and to identify the most successful treatment pathways for individual situations. An example of a research need in this area is to analyze existing data to determine efficacy of different medications approved for opioid addiction in combination with various psychosocial services and the intensity of ancillary psychosocial services. As another example, vaccines against opioids should be investigated as a potential longer-term strategy to treat opioid addiction. Development of these innovative modalities for treating addiction will build upon research findings on the biology and chemistry of opioid addiction, non-biological contributors to opioid addiction, and pain management.

- **Conduct research to inform development of best practices and guidelines for opioid addiction treatment in women who are or plan to become pregnant.** Research is needed to determine optimal approaches to medication-assisted treatment in pregnant women and new mothers with opioid addiction, as well as pharmacologic and non-pharmacologic treatments for babies born with neonatal abstinence. There is also a need for development of better methods to screen pregnant women for opioid misuse and to identify neonatal opioid abstinence syndrome in babies exposed to opioids in utero, as well as data on long-term childhood developmental outcomes.
- **Develop smart technologies to deliver care, support recovery, and monitor the impacts of pharmacological therapeutics.** An emerging area for research is the application of innovative technologies to the treatment of opioid addiction. Research is needed to explore the use of telemedicine and mobile interventions for monitoring and therapeutic applications and their impacts on opioid use and effectiveness as tools to support recovery.
- **Conduct research to inform the development and effective implementation of clinical best practices, guidelines, and standards for the treatment of opioid addiction.** Research has consistently shown that continuity of care is critical in the treatment of opioid addiction, but such continuity is the exception rather than the norm. Research is needed to increase uptake of clinical guidelines and best practices among providers and hospitals. Also, research is needed on ways to enhance treatment adherence and continuity from one stage of treatment to another. Additionally, research is needed to develop and evaluate the quality of coordinated care models and coordinated transition for patients recovering from overdose into appropriate treatments.
- **Enhance access to care through innovative strategies.** Access to care remains a primary barrier to treatment of opioid addiction, especially in rural communities and for certain populations, including pregnant and breast-feeding women. Research is needed to develop innovative strategies for providing access to addiction treatment outside of the traditional health system setting or specialty substance abuse treatment setting. For example, these innovative strategies may include novel peer engagement mechanisms or treatment settings (e.g., pharmacies, fire stations, faith communities, telemedicine, mobile integrated healthcare, facilities that allow mothers and children to stay together, and community paramedicine). Research on these innovative patient centered care models for engaging and retaining patients in treatment can ensure continuity of care and facilitate successful long-term outcomes.
- **Assess the effectiveness of peer recovery support services as a component of the public health response.** Peer workers who are in recovery from addiction are playing a growing role in the response to the opioid crisis by conducting outreach, engaging patients, and providing peer

recovery support services during and after treatment. Research is needed to accurately describe the various peer support approaches and to evaluate their relative effectiveness. Examples of recovery support services to be investigated include patient engagement in emergency departments and other settings; use of the workplace for peer support and recovery interventions; patient outreach and education; naloxone training and distribution; treatment linkage; and mentoring and coaching during and after treatment.

- **Determine how to integrate public health approaches into criminal justice settings.** There is a need for additional evaluation of approaches that integrate public health and public safety strategies. The impact of law enforcement, court, and corrections policies on illicit opioid use and addiction is still unclear, but implementation of evidence-based opioid treatment approaches in criminal justice settings will require greater understanding on points for intervention, effective training of personnel, and appropriate treatment strategies. Public health approaches are also critical to preventing opioid exposure to the first responders, including police, fire, and paramedics, who are on the frontline of the epidemic.
- **Evaluate the efficacy of faith-based recovery support services.** Faith-based recovery communities, housing and service providers of long-term recovery support and essential wrap-around services are becoming a more integral part of the continuity of care, as well as instrumental in the prevention of opioid use and misuse. There is also a growing movement of faith-based recovery support service providers partnering with rehab and clinical entities to offer greater access to medically assisted therapies. In order to continue to enhance patient choice and increase program participation by a greater variety of providers, we need to capture outcomes and measure the efficacy of faith-based recovery and social supports.

6. Overdose Prevention and Recovery

Goal Statement

The goals of research in opioid overdose prevention are to understand how to reduce opioid overdoses, both fatal and non-fatal, and increase the likelihood that people who overdose will survive and recover from opioid use disorder.

State of the Science

Research on overdose prevention and recovery has consistently demonstrated that the U.S. Food and Drug Administration approved opioid antagonist, naloxone, reverses overdose and has saved many lives when administered in time to individuals who have overdosed on opioids.^{55,56} It is clear that broader availability and use of opioid antagonists is a critical part of addressing the rising numbers of opioid overdose deaths, but the full impact of expanded naloxone use on opioid overdose morbidity and mortality is still to be determined. It is also clear that comprehensive addiction treatment following successful naloxone administration is critical for individuals to stop drug use and reduce their risks.⁵⁷ However, treatment access following an overdose is not assured, and many overdose survivors do not

⁵⁵ <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6106a1.htm>

⁵⁶ <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=236349ef-2cb5-47ca-a3a5-99534c3a4996&audience=consumer>

⁵⁷ <https://www.ncbi.nlm.nih.gov/pubmed/25919527>

obtain treatment.⁵⁸ Research has demonstrated that those who have survived an overdose are at increased risk for a subsequent overdose,⁵⁹ thus distribution of naloxone and successful transition to treatment immediately after overdose reversal are essential.

Research Gaps and Needs

Additional research is needed on: (1) strategies to enhance awareness in at-risk populations and clinical service providers (e.g., media campaigns, surveillance and early warnings of overdose outbreaks, naloxone deployment warnings); (2) educational interventions focused on healthcare providers, family members, first responders, and bystanders on safer opioid use, on appropriate use of opioid overdose antagonists and other interventions, and on opioid storage and disposal; (3) clinical care for suspected opioid overdose patients with and without antagonists by bystanders, users, family members, and first responders including law enforcement and health professionals in emergency settings, (4) improved surveillance of trends in opioid overdoses, to assure distribution and availability of appropriate products; (5) increasing access to overdose reversal products and services and improving timely delivery, and (6) strategies to increase successful engagement in opioid use disorder treatment following overdose reversal. More specifically, ongoing research and infrastructure development needs to advance our ability to prevent overdoses and assist in overdose recovery and should include:

- **Develop additional methods for preventing opioid overdose deaths, such as vaccines, devices, and novel medications.** Additional modalities could help prevent opioid overdose deaths both by reducing their occurrence and by improving the success of overdose treatment when opioid antagonists are not available. For example, overdose occurrence could be reduced through the use of devices and other technologies to test illicit opioids for the presence of substances that could substantially increase overdose risk (e.g., fentanyl analogues, benzodiazepines). Additionally, rescue breathing and other medical support modalities (e.g., pocket masks and bag valve masks) can sustain life when treatment with opioid antagonists is unavailable. Both clinical and nonclinical research is needed to identify vaccines and novel medications for overdose reversal, determine their efficacy, and develop best practices to educate individuals, care providers, and the general public on these methods.
- **Research communication strategies to enhance awareness of opioid overdose medication in at-risk populations and clinical service providers.** Naloxone is used by health personnel (e.g., EMS and emergency departments, primary care providers treating patients with long-term opioid therapy), law enforcement officials, and by family and friends of those at risk of overdose. However, naloxone administration training is quite varied among these care providers. Additional research is needed to identify and target best practices to each of these groups, tailored to their training and expertise, to better support their life-saving role in supplying or administering naloxone.
- **Identify and track trends in fatal and non-fatal opioid overdoses to inform distribution and availability of appropriate products and services.** A key to preventing overdoses is to accurately characterize trends in overdose occurrences through the use of various data sources, including public health, laboratory surveillance, poison center, EMS, clinical laboratories, law enforcement, medical examiner, and emergency department data. These data are needed to inform rapid detection of emerging trends in overdoses, enable evaluation of policy decisions

⁵⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27018626>

⁵⁹ <https://www.ncbi.nlm.nih.gov/pubmed/17554010>

related to fatal and non-fatal overdose occurrences, and adequately determine the need for opioid use disorder treatment.

- **Develop new tools and local capacity to detect, identify, and characterize novel synthetic opioids.** As novel compounds flood the illicit drug market, it is critical that advanced tools are available to rapidly detect, identify, and characterize these compounds and their associated physiological effects.⁶⁰ Research is needed to inform the development of tools that can rapidly and accurately detect trace amounts of novel compounds, on site and at the point of care, and predict their behavior, potency, and interactions with human biology. There is also a need to develop best practices for communicating with laboratories about the chemical and biological markers of novel compounds detected in the drug supply and to improve the capacity of localities to rapidly adjust testing protocols for use in clinical decision making and medicolegal death investigation.
- **Research appropriate access to, and delivery of, overdose reversal products and services.** Encouraging the broader use of opioid antagonists is complex and involves economic, scientific, public health, behavioral and legal dimensions. Many states have enacted laws concerning naloxone, such as legislation facilitating bystander administration and provisions mandating the co-prescription of opioids and opioid antagonists. Quantitative research may be able to identify the impact of these laws at the state level. Additionally, assessment of current delivery models for naloxone could help inform best practices for those working in emergency preparedness and policy formation. Research is also needed to assess the efficacy of current overdose treatment delivery models for high-potency fentanyl analogues and combinations of opioids and other central nervous system depressants. Such analyses could include a needs assessment for longer acting or higher dose antagonists.
- **Conduct research to identify factors associated with successful and unsuccessful long-term outcomes for people who have overdosed.** There is a need for longitudinal studies that collect and analyze information on the long-term effects of overdose in the recovery of patients over an extended period of time. It is imperative that longitudinal data comparing the outcomes of different forms of treatment and therapy are collected, analyzed, and interpreted to improve overdose prevention and recovery efforts. Such research can draw on All Payer Claims Databases, PDMPs, and other sources of longitudinal health information, to help identify risk and protective factors that impact the likelihood of long-term survival and recovery.
- **Assess and develop methods to safely detect and intercept illicit synthetic opioids:** Synthetic opioids are increasingly implicated in overdose deaths,⁶¹ and most of the supply of these agents is from overseas labs, with products brought to the US through international transportation and postal systems. Because of their relatively high potency (i.e. 100 or more times more potent than morphine for some fentanyl-related compounds),⁶² shipments of illicit synthetic opioids may be of relatively small quantities that are hard to detect. However, stemming the flow of this supply is a critical aspect of the Federal health response, not only to reduce overdoses but also to protect personnel who may be exposed to potentially harmful compounds through transport and inspection processes. Research should identify novel detection methods and technologies that

⁶⁰ <https://www.ncbi.nlm.nih.gov/pubmed/30165647>

⁶¹ <https://www.ncbi.nlm.nih.gov/pubmed/29715347>

⁶² <http://www.dtic.mil/dtic/tr/fulltext/u2/a199595.pdf>

enable rapid detection and identification of these compounds by laboratory networks and other approaches, for the safe and effective removal from the supply chain.

7. Community Consequences of Opioid Addiction

Goal Statement

Many American communities have been hit especially hard by the opioid crisis; individuals, families, neighbors, schools, and workplaces within these communities are facing challenging social and economic conditions as a result. The overall goals of research on the community consequences of opioid addiction are to help communities accurately assess the opioid crisis in real-time, effectively allocate resources, and successfully leverage existing systems and services. Research in these areas will help communities build sustainable solutions that account for their unique features and culture. This requires additional work in understanding and responding to the broader context of the opioid crisis.

State of the Science

Knowledge, understanding, and awareness of factors involved in the opioid crisis are rapidly evolving. Research has demonstrated that communities experiencing overall declines in health and well-being, and increased prevalence of pain and desperation may experience higher rates of opioid addiction and overdose.⁶³ Communities impacted by the opioid crisis report increases in child abuse and neglect; displaced and at-risk children, including those entering foster care systems and children prenatally exposed to opioids; lost wages and employment; crime; domestic abuse; homicide; and suicide.⁶⁴⁻⁷⁰ The estimated magnitude of the consequences of opioid addiction, illicit drug exposure, and fatal and non-fatal overdose have significantly outstripped resources, and are more pronounced in certain geographic locations and demographic groups (Figure 2). The burden of the opioid crisis—felt by hard-hit rural communities and now nationwide—has further taxed already stressed systems of mental health, social services, and criminal justice.^{71,72} People with disabilities appear to have difficulty accessing treatment for opioid use disorder. Barriers to access include treatment centers in rural communities are frequently not wheelchair accessible, policies that limit access to opioids without offering alternative pain management options, and limited insurance coverage.⁷³ Affected communities preparing for increased overdose and death due to opioids are reallocating resources to better support the services shouldering the heavy costs of the crisis, such as the education, early intervention and special education, foster care, healthcare, disability assistance, and criminal justice systems. The high

⁶³ <https://www.ncbi.nlm.nih.gov/pubmed/26575631>

⁶⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5640267/>

⁶⁵ <https://www.ncbi.nlm.nih.gov/pubmed/21392250>

⁶⁶ <https://www.childrensdefense.org/child-watch-columns/health/2017/children-and-the-opioid-crisis/>

⁶⁷ <https://www.ncbi.nlm.nih.gov/pubmed/29455851>

⁶⁸ <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1032.7009&rep=rep1&type=pdf>

⁶⁹ <https://www.ncbi.nlm.nih.gov/pubmed/27981691>

⁷⁰ <https://mpira.uni-muenchen.de/85712/>

⁷¹ <https://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.htm>

⁷² <https://www.ncbi.nlm.nih.gov/pubmed/21392250>

⁷³ <https://acl.gov/sites/default/files/news%202018-05/20180502NIDILRROpioidRFIFindings.pdf>

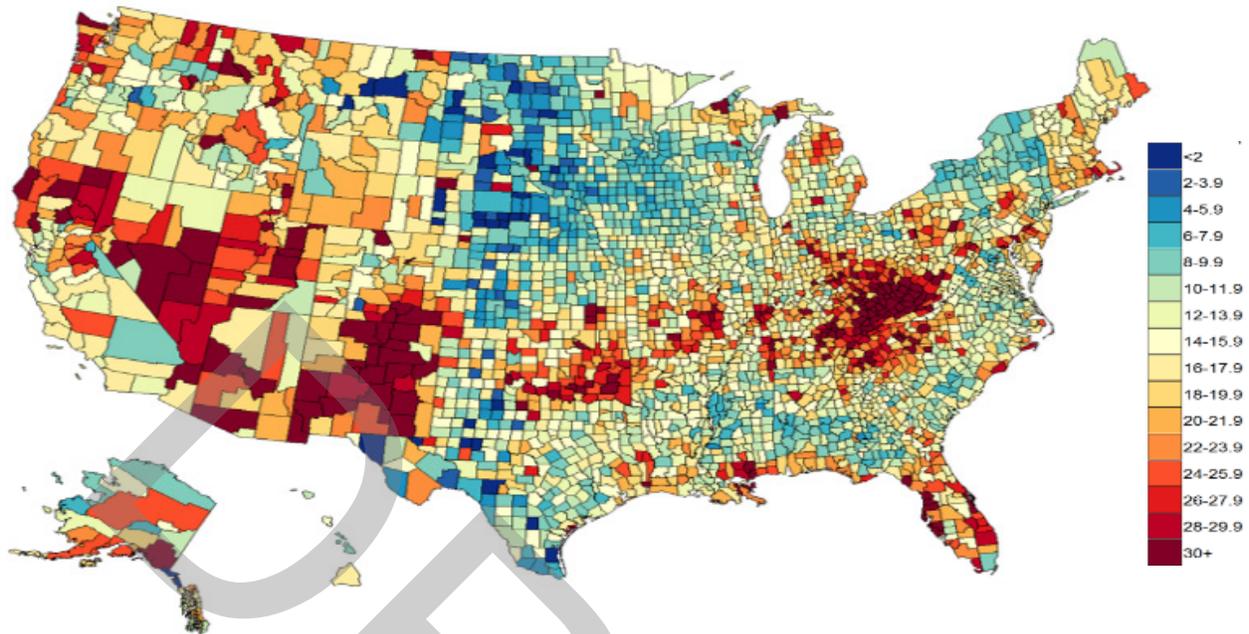


Figure 2. Drug Overdose Rates Vary Across the United States: Estimated Age-adjusted Death Rates per 100,000 for Drug Poisoning by County in 2016. Source: <https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm>

addiction and death rates are having a significant impact on the workforce at a time when workforce demands are beginning to accelerate. Meanwhile, environmental contamination due to opioids through wastewater is of potential concern and is poorly understood.^{74,75} While many long-term consequences of the current opioid crisis are still unknown, viable research, surveillance, and technology solutions to meet the varying community needs and support broader community resilience goals are beginning to emerge.

Research Gaps and Needs

The consequences felt by communities nationwide are exacerbated by underlying structural issues, including poor access to care, limited occupational opportunities, social isolation in hard-hit areas of the country, and stigma.^{76,77} Research investments into the consequences of the opioid crisis should account for the historical, steady decline in community health and well-being that helped to fuel the current situation. Technologies to ease data and knowledge sharing are necessary to assess the current crisis and mitigate future problems. Research, data, and information sharing are necessary to focus resources and mitigate consequences to communities, including public health, social systems, and law enforcement and international interdiction efforts. Concerted efforts should focus on advancing knowledge and capabilities to:

⁷⁴ <https://www.ncbi.nlm.nih.gov/pubmed/29727969>

⁷⁵ <https://www.ncbi.nlm.nih.gov/pubmed/26190693>

⁷⁶ <https://www.ncbi.nlm.nih.gov/pubmed/26575631>

⁷⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5640267/>

- **More quickly and accurately assess opioid morbidity and mortality.** The ability to rapidly collect, analyze, and integrate real-time public health surveillance, laboratory, law enforcement, emergency department, and medical examiner data is necessary to monitor community health and well-being, guide resource allocation including mental health services, and foster community resilience. Naloxone administrations obtained from emergency medical services (EMS) patient care records may serve as a useful proxy for overdose surveillance in individual communities and might be a previously unused data source to describe the opioid epidemic, including fatal and nonfatal events, on a national level.⁷⁸ Novel approaches to timely and accurate assessment of the impacts of the opioid crisis on public safety, medicolegal death investigations, drug exposures (including prenatal exposure), crime, and infectious disease spread are needed. Research and data that identifies factors contributing to quantifiable economic impacts on communities is needed to assist in developing strategies for health, child welfare (e.g., child protective services), and criminal justice systems at both state and local levels.
- **Identify how public health resources can be effectively allocated with the goal of long-term sustainability.** Research is needed that evaluates public health surveillance, medical, and economic data that could assist in resource allocation for better community outcomes with more long-term sustainability. Resources must be allocated to data, tools, and surveillance that produce results.
- **Identify how existing public health system actions, services, and partnerships can be leveraged to build resilience in communities impacted by the opioid crisis.** Best practices and case studies or examples of successful interventions can be documented to establish the basis for new and improved interventions.
- **Determine the efficacy of innovative and creative approaches to the opioid response that address a community's unique features and culture.** Research programs must be designed to include, consider, and capture data on specific factors such as geography, demographics, socioeconomic status, and access to services that impact response to the current crisis, but also account for community well-being and resilience. Interactions among such factors, including the role of disability (and disability policies) in affecting the economy in some areas, need to be measured and studied as potential causes and consequences of the opioid crisis. Research is needed to better understand causal mechanisms and to leverage science and technology innovations to address factors that play a significant role in the crisis.
- **Examine the vulnerabilities of children residing with opioid-addicted caregivers, including developmental delays and addiction trajectory.** Children with opioid-addicted caregivers are particularly vulnerable to long-term negative consequences of the opioid crisis. Research should examine the risk factors for developmental and psychological delays in this growing population. This research can also include the long-term outcomes of prenatal exposure to opioids.
- **Evaluate the role of recovery community organizations in mitigating community consequences of opioids.** Recovery community organizations, including faith-based recovery communities, serve not only individuals with or in recovery but also the broader community. Research is needed to fully understand the range of community roles they play and their impact on the communities they serve.

⁷⁸ <https://www.cdc.gov/mmwr/volumes/67/wr/mm6731a2.htm>

- **Determine the fate and transport of opioid and opioid metabolites in the environment.** A large percentage of opioids and their metabolites are excreted in urine, which ends up in the wastewater treatment system. The impacts of these releases on ecological health is unknown.

8. Opportunities for Enhanced Coordination

The complexity of the opioid crisis demands a response that spans multiple facets of government and utilizes the expertise and resources available in both the public and private sectors. The Federal Government should expand coordination of surveillance, research and implementation efforts both between Federal agencies and through enhanced interactions with non-Federal stakeholders such as State, local, territorial, and Tribal governments, industry, nonprofit community organizations, and academic researchers. Such coordination efforts provide opportunities to strengthen lines of communication;⁷⁹ identify and share best practices;⁸⁰ streamline research funding and program implementation processes;⁸¹ expand, improve and coordinate data collection activities;^{82,83} and leverage existing resources more effectively and distribute them more efficiently and equitably.

While Federal coordination, both among agencies and across sectors, could enhance all research efforts described in this roadmap, collaboration is particularly critical to help advance and implement essential research components that may be underrepresented in the research enterprise but are fundamental to the success of the response. These components include consideration of special populations (e.g., children, people living with disabilities, pregnant and breast-feeding women, justice-involved populations), geographic disparities (e.g., rural versus urban needs and challenges), and data collection and information sharing. By incorporating these components into coordinated research endeavors, the Federal Government can support research efforts and investments that reflect the complexity of the opioid crisis landscape.

An effective health S&T response to the opioid crisis should not be limited to research activities. Collaborative and coordinated efforts across stakeholder groups should also strive to improve the efficacy of dissemination and education activities, such as training, public awareness campaigns, and educational literature. These efforts are critical to sharing the latest research results and ensuring that new knowledge and best practices are leveraged to improve on-the-ground prevention and response efforts.⁸⁴ Such activities are especially important given the rapid developments in both the crisis itself and in our understanding of opioid-related health S&T.⁸⁵ Dissemination and education should be targeted toward health care providers, emergency personnel, and policy professions, as well as toward the general public.^{86,87} Possible dissemination and education activities include guidelines for

⁷⁹ <https://www.nga.org/letters-nga/opioid-crisis-legislation/>

⁸⁰ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

⁸¹ <https://www.nga.org/news/press-releases/governors-release-recommendations-for-addressing-opioid-epidemic/>

⁸² https://minorityhealth.hhs.gov/Assets/pdf/ACMH_Recommendations-12-27-2017.pdf

⁸³ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

⁸⁴ <https://www.ncbi.nlm.nih.gov/pubmed/29023083>

⁸⁵ <https://addiction.surgeongeneral.gov/sites/default/files/surgeon-generals-report.pdf>

⁸⁶ <https://www.ncbi.nlm.nih.gov/pubmed/29023083>

⁸⁷ https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf

continuing medical education curricula and national media campaigns on risks of opioid addiction. Specific collaboration mechanisms with the potential to benefit the opioid crisis response include the following:

- **Align related research funding opportunity announcements.** Interagency coordination with regard to funding opportunities may reduce application burden,⁸⁸ expand interdisciplinary research opportunities, and mitigate redundancies in the Federal research portfolio. Opioid-related research could be advanced through joint or coordinated funding opportunities across agencies, such that timelines and topic areas are more efficiently aligned.
- **Establish a Federal opioid crisis research community of practice.** Agencies involved in the Federal opioid research response would benefit from the creation of a forum for regular, sustained engagement to discuss common goals and challenges, identify opportunities for coordination of programs and resource allocation, and share key insights and findings. An immediate priority of the community of practice should be ensuring that results of Federal opioid health research are, to the extent feasible, released in a timely and open manner. Adherence to open data principles will accelerate research and diffusion of best practices.⁸⁹
- **Promote additional coordination of the public health community with law enforcement and other justice systems working to address the opioid crisis.** Public health, law enforcement, and other justice systems are working to address the opioid crisis, but collaboration between actors working in these areas has been relatively limited. Enhanced coordination between these groups might afford additional opportunities to connect individuals at high risk for opioid overdose with addiction treatment and other social services.⁹⁰ There is a need for additional research that describes existing public health-public safety practices and programs, assesses their efficacy, and capitalizes on that knowledge to enhance the effectiveness of existing programs and develop new, innovative collaborations. While much of the coordination will be executed locally, the Federal Government can support the necessary research and develop evidence-based guidelines and best practices in these areas.

Conclusion

Many Federal departments and agencies have substantial research efforts related to the opioid crisis, and strategic coordination of those efforts is critical to ensuring that the Administration delivers the comprehensive science response that the opioid crisis demands. The Opioid FTAC collated and analyzed current Federal initiatives and programs in this area; assessed data needs, knowledge gaps, and challenges to implementation and coordination; and identified investments and research activities to address the gaps and needs. Moreover, the FTAC provided a forum for interagency discussions that may lead to closer coordination of strategy and activities. While this Roadmap represents an important step, continued coordination of the Federal science and technology enterprise and engagement with private, state, local, Tribal, territorial, and non-profit stakeholders, including faith-based organizations, is essential for long-term resolution of the opioid crisis.

⁸⁸ <https://www.nga.org/news/press-releases/governors-release-recommendations-for-addressing-opioid-epidemic/>

⁸⁹ <https://www.federalregister.gov/documents/2013/05/14/2013-11533/making-open-and-machine-readable-the-new-default-for-government-information>

⁹⁰ <https://www.ncbi.nlm.nih.gov/pubmed/29414484>

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