

The American Opioid Epidemic in Special Populations: Five Examples

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The United States is in the midst of an unprecedented crisis of prescription and illicit opioid misuse, use disorder, and overdose. In 2018, nearly 47,000 Americans died from an overdose involving opioids [174]. In 2018, 10.3 million people aged 12 years and older reported misusing prescription opioids or using heroin, and 2 million met the diagnostic criteria for having an opioid use disorder in the past year—lower than 2015 through 2017 [150].

Although the crisis has affected large swaths of the U.S. population, it has affected certain segments of the population with an extra level of intensity—justice-involved populations, rural populations, veterans, adolescents and young adults, and persons who inject drugs. Other than for persons who inject drugs, little research to date has been dedicated toward understanding the specific needs of these special populations, including building the evidence base for targeted approaches and solutions. Research has clearly shown that solutions for the opioid overdose epidemic are not one size fits all, and special attention should be paid to these populations that may be suffering unduly. For each identified population, this manuscript reviews why it is an important area of focus, current barriers encountered in accessing care, promising ap-

proaches in supporting this population, and high-impact research and action priorities.

Justice-Involved Populations

The Importance of Justice-Involved Populations

Economic decline, incarceration, and drug-related mortality are tightly connected at a population level [124]. More than ten million people pass through the justice system each year and over two million people are confined in U.S. jails or prisons daily [90]. Among those who encounter the justice system, rates of opioid use are significantly higher than in the general population [175]. This linkage is not surprising: possession and use of many drugs are illegal and people who experience substance use disorder may commit crimes in order to acquire their desired addictive substance.

Justice involvement may include a range of experiences, including detention in local jails, state prisons, or federal prisons, as well as monitoring while in the community as part of community corrections (i.e., probation and parole). From 2007 through 2009, more than a quarter of those who were detained in state prisons or jails reported a history of opioid use [23]. In the intervening years, rates of opioid use and over-

dose have risen sharply [150], suggesting that the current rates of illicit opioid use and opioid use disorder (OUD) among individuals involved in the justice system are likely significantly higher in 2020. Another recent analysis also demonstrated that as the intensity of opioid use increases, the likelihood of justice involvement increases [175]. Further, a recent review of fatality records found that individuals with adjudicated arrest records experienced fatal overdoses at a significantly elevated rate relative to state residents without arrest records [58].

Given the high prevalence of substance use in justice-involved populations, including opioid use and OUD, jails and prisons represent one of the largest providers of treatment for substance use disorders (SUDs) in the United States and a location where evidence-based interventions and solutions could make the biggest impact.

Barriers to Treatment for Justice-Involved Populations

Prisons and jails present different challenges in ensuring provision of care to those in detention. In particular, most jail stays are relatively short compared to the many years individuals typically spend in prison. The average jail stay in 2016 was 25 days [180], which poses challenges for screening and initiating treatment, as well as a risk of disruption of ongoing treatment. It is therefore important that as individuals are being processed toward a jail stay, substance use treatment needs are identified and appropriate care is provided, including continuity of any treatment that an individual may have been receiving prior to their arrest. Timing of release from jail can also be unpredictable for short stays, particularly for people being held prior to a conviction (i.e., “pre-trial detainees”), leading to further challenges in ensuring continuity of care. Jails are typically managed at a county level, which can result in significant resource challenges due to a lack of federal funding. Nonetheless, many jails across the United States are embracing these challenges and developing new models for providing medications for opioid use disorder (MOUD) in this dynamic environment. In the coming years, new data should be available to provide insight into how effective these models are.

For longer stays in both jails and prisons, concerns about costs of treatment, logistics of providing care (e.g., sufficient staff with buprenorphine waivers or regulatory barriers to establishing a jail-based methadone opioid treatment program), and long-standing

negative and stigmatizing attitudes toward addiction in general and opioid agonist treatments (methadone and buprenorphine) in particular present critical challenges to providing treatment for OUD within the justice system [59].

Continuity of care is essential as people exit the jail and return to their community. This transition is a critical period of vulnerability for people with OUD. Overdose-related mortality risk is very high (130-fold increased risk during the first weeks of re-entry) as individuals exit the jail and return home [14]. Ensuring continuity of care during re-entry requires relationships between justice systems and community-based providers, including managing cross-agency information sharing. It is also critical to address the logistics of helping individuals navigate what can be a chaotic time, as life chaos is predictive of poor general health outcomes in justice-involved populations [155]. In addition to trying to connect to treatment and rebuild relationships, individuals returning to their community must secure housing and jobs, and comply with other probation and/or parole requirements. Further, the needs of individuals with OUD tend to be quite complex; mental and physical health comorbidities, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV), are common in this population [112]. In addition, electronic records in prisons and jails are relatively rare, and thus it can be difficult to acquire records of treatment received during periods of incarceration.

Justice-involved individuals may experience numerous obstacles when trying to access treatment in their communities, including lack of insurance or limited community capacity to provide MOUD. These challenges may be exacerbated by the stigma of both their addiction and their involvement in the justice system. Justice-involved individuals are less likely to have health insurance coverage, though recent data suggest that the expansion of eligibility under the Affordable Care Act has reduced these disparities [93]. Even in outpatient treatment for OUD, justice-referred individuals are only one tenth as likely as their non-justice-involved peers to receive agonist MOUD [96]. Even when MOUD is offered, whether in jails and prisons or in communities, it is rare that patients are offered all three FDA-approved options (naltrexone, methadone, buprenorphine); less than 3% of community-based treatment centers have the capacity to offer all three medications [83]. Further, it is typical to experience significant delays when trying to set up appointments

with community-based providers, and these delays in treatment can lead to a return to use of opioids.

Promising Approaches

Ensuring access to MOUD for justice-involved populations is important both when people are incarcerated as well as when they have returned to their communities. A smooth connection to community-based services as individuals are being discharged from incarceration can dramatically reduce the risk of opioid-related mortality upon community re-entry [68]. Most jails have been historically reluctant to offer MOUD, though there have been some exceptions, including Rikers Island [104] and jails in Connecticut, New Mexico, and Rhode Island. Often, however, these programs have been characterized by offering only a single medication, rather than all three FDA-approved forms of MOUD. This has slowly begun to change, with positive results. For example, in 2017, Rhode Island implemented a policy of allowing all detainees in the state with OUD access to MOUD and saw a 65% reduction in overdose deaths of justice-involved populations, which drove a 12% reduction overall in statewide overdose deaths [68].

An important aspect of the Rhode Island model is that it offered all three FDA-approved medications to patients, allowing them to choose the medication best suited to their needs. When offered this choice, almost none selected naltrexone. It is interesting that so few patients selected naltrexone when given the opportunity to select their preferred treatment. Many jail administrators prefer naltrexone and may offer this as the only MOUD [59]. This preference is due in part to a view that naltrexone is an “opioid-free” treatment option, as it is an opioid antagonist treatment, as opposed to opioid agonists like buprenorphine (partial) and methadone (full). There are also pragmatic reasons for this preference among jail administrators: unlike buprenorphine and methadone, naltrexone does not require special training or approvals for medical staff to deliver and is perceived as low-risk for diversion in secure settings. Even so, these considerations must be weighed against the fact that naltrexone does not have as robust of an evidence base as methadone and buprenorphine in justice settings [105]. Naltrexone has been shown to have a benefit for those who can be successfully inducted [99,105], but many people are not successfully inducted, and successful induction can be particularly challenging in jail settings, where stays are very brief.

Other promising approaches focus on re-directing people with an SUD away from the justice system, and in particular reducing the number of people incarcerated for drug-related offenses and connecting them instead to treatment. This process may not only save lives, but also result in significant cost savings [97]. This re-direction has begun to happen through policy changes at both state and local levels. Police-led programs such as Law Enforcement Assisted Diversion (LEAD) and the Police Assisted Addiction and Recovery Initiative (PAARI), which assist in directing individuals with SUD to treatment rather than into the justice system, have emerged and grown rapidly in recent years [66].

Innovative practices in drug courts also show promise. Like jails, many courts have been historically opposed to MOUD treatment, but this is changing. The National Association for Drug Court Professionals released guidance in 2019 encouraging drug courts to offer all three forms of MOUD [121]. In New York, an innovative Opioid Intervention Court model focused on developing best practices for people with OUD has demonstrated promising results by embracing MOUD [171]. The utilization and prescription of MOUD in justice settings not only reduce mortality but are also potentially very cost effective.

Another promising tool for reducing overdose mortality is providing overdose education and distributing naloxone in justice settings. Community re-entry is a period of heightened risk for overdose and providing naloxone may significantly reduce risk during this time [22].

Research and Action Priorities for Justice-Involved Populations

To improve care for justice-involved people, it is important to develop processes to systematically identify treatment needs and connections to care prior to incarceration, while incarcerated, and upon return to the community.

Drug courts divert people with OUD to treatment. On average, drug courts reduced participants’ drug-related recidivism from 50% to roughly 37% up to three years post-court [114], although success often depends on characteristics of the patient’s case, staff quality [140], and availability of nearby MOUD providers [109]. Of note, 55% of drug courts in 2010 were located in rural areas [109]. Although drug courts are a promising approach to ensure that those with OUD receive treatment instead of detention, there are still sig-

nificant barriers to integrating MOUD into drug courts, and these barriers must be addressed for drug courts to reach their full potential. Research focused on standardizing quality of treatment and ensuring standardized support infrastructure through drug courts could significantly advance the effectiveness of this intervention.

It has not been standard practice to offer MOUD in jails and prisons, but several court rulings in 2019 suggest that this may rapidly change. Rhode Island offers a powerful example of the potential of this approach, though the state has a relatively uncommon structure in that its jail and prison systems are unified. However, other states are following Rhode Island's lead. In 2019, Massachusetts launched an effort in seven counties to offer all three FDA-approved MOUD for use in jails. The initiative, which includes treatment initiation and continuation during incarceration, and continuation of treatment upon return to the community, represents an important partnership between justice-involved stakeholders and community-based providers. This effort is being studied through a partnership with researchers, as part of the Justice Community Opioid Innovation Network (JCOIN). The National Institute on Drug Abuse (NIDA) has committed \$145 million over five years to support this study and others like it, in an effort to evaluate the effectiveness of novel approaches to partnering justice and community-based stakeholders to address opioid use in justice-involved populations.

To address the challenges of continuity of treatment, it is critical that services and needs are coordinated as the individual exits the jail and returns to their community. One option is low-threshold approaches to treatment, including models that bring care to individuals via mobile vans, peer recovery support, and immediate access to MOUD [95]. Another promising approach is data-driven collaborations between justice systems and community-based health care providers that could provide a powerful tool for reducing gaps in care. It is critical to ensure continuity of care and engagement in care in the community, as both have been associated with reductions in criminal activity. Suspending Medicaid coverage, rather than terminating it, helps facilitate continuity of care after release [79]. Some states are further experimenting with Medicaid Managed Care organizations to facilitate continuity of treatment after release [165].

The risk of relapse upon community re-entry could be significantly reduced if people with OUD were of-

fered MOUD during incarceration. Risks could be further reduced if MOUD and naloxone were provided upon release, along with a 'warm handoff' to a treatment facility and social services. This continuous care approach is an important tool for addressing the public health and public safety risks that emerge during transitions between justice-involved and community settings.

Attending to OUD in justice-involved populations requires attending not just to their substance use problems, but to the full spectrum of their needs, including comorbid physical and mental health needs. Thus, effectively addressing substance use within justice-involved populations requires a multi-level (or multi-system) approach, engaging multiple organizations within a community (e.g., jails, substance abuse treatment, behavioral health providers, and general medical care). Even within a jail, multiple vendors may provide services and require significant effort to coordinate, so often individuals who are incarcerated receive fragmented care throughout their stay. The Transitions Clinic model, which focuses on providing health care in primary care settings for people returning to communities, is a promising model for truly integrated care [166]. In short, partnerships between community-based health and justice systems are essential to effectively improving outcomes for this population, which drives many of the societal costs of the opioid epidemic.

Examples of specific research and action priorities could include:

1. Initiating and continuing medications for opioid use disorder while individuals are detained or incarcerated, including through the use of telemedicine, and ensuring that medication for opioid use disorder is not interrupted when the individual returns to the community.
2. Supporting the prescription of buprenorphine and methadone (agonist therapies) over naltrexone (antagonist therapy), absent well-designed comparative effectiveness trials that provide evidence of equivalent or better outcomes with naltrexone, and improving education efforts on these therapies to reduce stigma.
3. Pursuing regulatory adjustments that would allow for suspension, rather than termination, of Medicaid when an individual enters a jail or prison, and supporting pilot projects to work with Medicaid Managed Care organizations to facilitate continuity of treatment.

4. Addressing logistical barriers to providing care by, for example, ensuring appropriate numbers of staff with buprenorphine waivers to care for the entire incarcerated population, and addressing regulatory barriers that stand in the way of establishing jail-based methadone treatment programs so that individuals do not need to leave the jail to receive medications for opioid use disorder.
5. Expanding drug court models to require both provision of medications for opioid use disorder and additional social services, and focusing research on establishing standards for consistency and quality between drug courts.
6. Partnering with community organizations to provide employment opportunities for those transitioning out of incarceration and on medications for opioid use disorder, as stable employment has been shown to lead to better overall outcomes.
7. Providing naloxone and naloxone education when an individual is released from incarceration to prevent against accidental death due to overdose.
8. Pursuing legal and regulatory changes that would reduce total and overall incarceration duration for people with opioid use disorder who have not been charged with violent or other serious offenses.
9. Ensuring that individuals who receive treatment for addiction in justice-involved settings also receive care and support for other needs, including health care and mental health needs.

Rural Populations

The Importance of Rural Populations

For the 18% of Americans living in rural communities¹, the national opioid epidemic exemplifies the “nonmetropolitan mortality penalty” [46], or the broad and growing phenomenon of higher death rates among rural versus urban populations [65]. The authors of this manuscript use the terms “rural” and “nonmetropolitan” interchangeably, in line with the Federal Office of Rural Health Policy (FORHP) in the Health Resources and Services Administration. FORHP designates areas as rural using components of both the U.S. Census Bureau definition of “rural” and the Office of Management

¹ For the purposes of this manuscript, “rural communities” are those where all population, housing, and territory is not within an urban area.

and Budget definition of “nonmetropolitan.” When citing research, the authors of this manuscript use the term employed in the source material.

Drug overdose deaths grew 325% in nonmetropolitan areas, compared to 198% in metropolitan areas, between 1999 and 2015, leading to deaths per 100,000 of 17.0 in rural and 16.2 in urban areas [103]. Despite a decline in opioid prescribing dating back to 2015, rural opioid prescribing rates continue to be higher than urban counterparts at both the individual and community levels [54]. Patients in the most geographically isolated rural counties were 87% more likely than counterparts in large metropolitan counties to receive an opioid prescription between 2014 and 2017 [64]. In 2017, 14 of the 15 counties with the highest opioid prescribing rate were rural [31,64]. More opioid prescriptions in rural areas ultimately contributed to more prescription opioid-involved deaths than in urban areas [36].

Opioid-involved deaths do not affect all rural communities equally. Counties facing greater economic distress have higher drug overdose mortality rates than more stable areas [115], contributing to increased deaths among rural [143] working-class whites. Recent research also suggests that the “nonmetropolitan mortality penalty” exacts a greater toll among high-poverty rural communities [47]. This may help explain the clustering of rural opioid-involved deaths from 2012–2016 in states (e.g., New Mexico, Utah) and regions (e.g., central Appalachia) [135] with more rural poverty. However, the pattern does not hold in rural New England, where fewer individuals live in poverty but more per capita die from opioids than in other regions, or the rural South, where more individuals live in poverty but fewer die as a result of opioid misuse [135].

Barriers to Treatment for Rural Populations

Rural populations face numerous barriers to treatment, including a lack of appropriate providers and opioid treatment programs (OTPs) and complications due to relatively smaller social networks and greater transportation distances to treatment. Compared to their urban counterparts, rural residents often travel longer distances to health care, including more than 20 miles to specialized treatment for OUD in Kentucky [25]. Compounded by transportation barriers, geographic distance can jeopardize rural patients’ ability to adhere to the requirements of MOUD [135].

In 2017, 56% of rural counties lacked a physician with a Drug Addiction Treatment Act (DATA) 2000 waiver (commonly known as the Drug Enforcement

Administration [DEA] X waiver), which allows them to prescribe MOUD, compared to 23% of urban counties [6]. The recent inclusion of certain non-physician practitioners (NPPs) as waived providers [161] expanded treatment availability in 43 rural counties [6]. However, 28 states prohibit certain NPPs from prescribing buprenorphine without a waived supervising physician [117], which does not remove the barrier that allowing NPPs to prescribe buprenorphine was intended to reduce. In 2017, 47% of rural counties had no waived provider of any kind [6]. The significant lack of physicians able to prescribe MOUD to those with OUD is a clear barrier to the ability of rural communities to access treatment for OUD.

Further, in 2011, 88.6% of nonmetropolitan counties had a shortage of federally certified OTPs compared to a shortage in 68.6% of metropolitan counties [55]. Residents of rural counties in five states had to drive 40 minutes longer than their urban peers to reach an OTP in 2017 [88]. Only 10% of OTPs were located in rural areas as of February 2019 [148]. The availability of fewer treatment providers in rural communities likely contributes to worse consequences for opioid misuse than in urban communities [103]. To address this, recently proposed regulations from the DEA would ease registration requirements for OTPs that dispense methadone in remote locations [56]. Satellite OTPs located in rural communities or MOUD delivered via mobile vans sponsored by urban OTPs could improve treatment availability in rural and other underserved communities.

Social networks tend to be much closer-knit in rural than in urban communities, and these relationships facilitate faster and broader diversion of prescription opioids for misuse [91,129]. More intimate community relationships are also associated with higher opioid prescribing rates among rural providers [41]. Lack of anonymity and higher chances of personal recognition likely contribute to the stigma that may also hinder rural patients, particularly pregnant women, from seeking treatment, especially in highly visible, traditional delivery settings for behavioral health care [78,132].

Promising Approaches

When naloxone is more readily available and those who have it know how to use it, overdose mortality can decrease significantly. Access to naloxone led to 26,463 reported overdose reversals in June 2014, an increase of more than 160% from 2010 [172]. Various individuals and organizations have effectively distrib-

uted naloxone in rural communities, including community-based programs, pharmacies, first responders, bystanders, and harm reduction programs such as syringe service programs (SSPs) [53,118,170]. Sometimes called “needle exchange” or “syringe exchange,” SSPs provide access to clean and sterile equipment for the preparation and use of drugs in order to lower the frequency of syringe sharing and reuse and the transmission of infectious disease via risky injection practices. SSPs also seek to reduce instances of drug overdose through overdose education, naloxone distribution, and information sharing on overdose prevention strategies. Comprehensive SSPs provide additional social and medical services, such as vaccinations, referral to treatment, and health education. In 2013, only 20% of SSPs were located in rural areas [53]. Expanding comprehensive SSPs to more rural communities can prevent opioid-involved overdose deaths and may also help reduce related infections, primarily HIV and HCV, among people who inject drugs [26].

Emerging evidence suggests that telehealth may help rural communities overcome limited geographic access to OUD treatment, particularly in accessing buprenorphine [102]. Following the requirements of the Ryan Haight Act of 2008, distant-site waived providers assess patients and prescribe buprenorphine via technology, often through a pharmacy that delivers the medication to the patient and manages refills with the prescriber electronically or by phone. Telehealth technologies also allow waived prescribers to monitor treatment adherence and behavioral health providers to furnish individual or group counseling and other behavioral therapies [28]. Providers have delivered effective buprenorphine treatment to rural patients via telehealth with similar or better outcomes in opioid abstinence and treatment retention compared to in-person care [57,181].

The hub-and-spoke model is an approach to furnishing MOUD that directs rural patients through a network of specialized, often urban, OTPs (“hubs”) providing daily support for patients with complex addictions and local waived providers (“spokes”) offering ongoing OUD treatment in community-based office settings [38,75]. In Vermont, the model increased the number of waived physicians by 64% and patients served per waived provider by 50% between 2012 and 2016 [24]. Eighty patients receiving MOUD through the model in 2017 reported 89% fewer emergency visits and zero overdoses over 30 months, on average [134]. The model also connects rural providers to vital practice

supports delivered in person or via technology (e.g., Project ECHO) [38,94].

Where patients with OUD rely on primary care physicians for access to MOUD, integrated behavioral health and primary care can provide coordinated, multidisciplinary services to more patients [98]. For example, when Health Resources and Services Administration-funded health centers integrated primary care, mental health, and OUD services, the number of rural patients who received MOUD at health centers nationwide increased 67% between 2016 and 2017. However, significant challenges related to reimbursement threaten integrated primary care treatment for OUD. For example, despite reimbursing federally certified rural health clinics (RHCs) for integrated care management for patients with behavioral health conditions, including SUD [34], the Centers for Medicare & Medicaid Services (CMS) does not consider furnishing MOUD to be a “primary care service” for primary care practitioners at RHCs. CMS requires RHCs to be “primarily engaged” in primary care services [35], defined as at least 51% of the total operating schedule, in order to receive enhanced, cost-based reimbursement for Medicare and Medicaid services. In this context, expanding delivery of MOUD could put some of the 4,500 RHCs at risk of losing their certification and the enhanced reimbursement meant to ensure financial stability and access to care in rural communities.

Clinical guidelines recommend MOUD for pregnant women who use opioids to avoid premature labor, fetal distress, miscarriage, and other adverse events for mother and baby that may result from withdrawal or abrupt abstinence from opioids, including neonatal abstinence syndrome (NAS) [151]. One way to improve outcomes for this patient population is deliver integrated prenatal care as early as possible during pregnancy and MOUD to reduce opioid cravings and withdrawal symptoms [151]. Coordinated prenatal care and MOUD helps to effectively and safely manage opioid dependence for rural opioid-dependent pregnant women while resulting in less severe NAS [87]. Coordinated services in rural Vermont from 2000 to 2006 reduced gestational age at MOUD treatment initiation from 22 to 4 weeks and led to 42% fewer newborns requiring treatment for NAS [111].

Research and Action Priorities for Rural Populations

Reducing the demand for opioids could reduce OUD, particularly among rural adolescents who are at higher risk for nonmedical prescription opioid misuse than

their urban peers [116,128]. Although there are no evidence-based models of care for treating adolescents with OUD [38], rural youth may benefit from brief universal prevention efforts (e.g., Strengthening Families, Life Skills® Training), which address rural-relevant risk and protective factors [116] and reduce initiation of prescription opioid misuse.

Additional treatment capacity for OUD in rural communities could start with encouraging existing waived providers to prescribe to more patients [144]. Waivered physicians in Vermont treated only 10% of the maximum possible patient load in 2014 [141]. Recent legislation allows certain newly waived physicians to treat 100 patients rather than 30 [161]. Previous evidence suggests the higher patient limit for more rural waived physicians could increase dispensed buprenorphine per capita by 11 times [144]. Consultation, training, mentoring, and other institutional and practice supports to address rural physicians’ concerns about prescribing MOUD are one way to increase rural providers’ patient load [6,38].

Physicians often request increased reimbursement and other financial incentives as another way to increase MOUD prescriptions. Recent reports indicate that health networks and insurance companies are piloting value-based payment and incentives for delivery of MOUD [75]. Previous research has documented improvements in care and reductions in cost for value-based payments in behavioral health care [146].

Chronic pain also more often afflicts rural residents than their urban peers [52]. Opioids will likely continue to be prescribed in large amounts in rural settings until there are accessible and affordable alternative treatment options for chronic pain in rural communities [70,128]. These treatment alternatives could include psychological and other non-pharmacologic interventions, though access to alternative pain management therapies remains limited, particularly in rural communities [142,156]. Until non-opioid approaches to pain management are more prevalent in rural areas, multicomponent adherence to prescribing guidelines and robust prescription drug monitoring programs may minimize adverse effects [130,176].

The national epidemic of opioid-involved overdose deaths has evolved over time in three waves, with deaths primarily attributed first to prescription opioids, then heroin, and, most recently, synthetic opioids [29]. A similar pattern holds in rural areas, where communities could benefit from addressing SUD more broadly. Rural deaths involving prescription opioids

declined from 2016 to 2017 [138] as prescription opioids became less available. Instead, rural residents turned to heroin [45] and fentanyl [39], but also non-opioid substances, particularly psychostimulants. For example, methamphetamine contributed substantially to nonmetropolitan drug overdose deaths from 2015 to 2016 [103], and in 2017 contributed to more deaths in rural (4.0 per 100,000) than urban (3.1 per 100,000) areas [74].

The national response to the opioid epidemic may require new flexibilities to address underlying substance use challenges regardless of the particular substance. This could mean federal policymakers loosening the restrictions on current opioid-specific funding to address SUD more broadly or appropriating new dollars with more inclusive authorities to address other substances. Congress did just this in recent funding for the Rural Communities Opioid Response Program administered by the Health Resources and Services Administration [139]. New flexibilities could also mean a focus on clinical and community interventions that address SUD more broadly, such as wraparound services, cognitive-behavioral therapy, contingency management interventions, and community reinforcement approaches [123]. Rural communities would likely need additional resources and technical assistance to implement these interventions.

Long-term recovery from substance use may depend on positive changes in the underlying social and economic conditions in many rural communities. Sustainable rural opioid responses could address economic challenges and associated mental health distress [115,143] and adverse childhood experiences [37] that often lie at the root of addiction. This may require national initiatives as well as state and local place-based interventions featuring comprehensive approaches to treatment and recovery services that address transportation, housing, job training, and other social determinants.

Examples of specific research and action priorities could include:

1. Continuing financial and technical assistance support for rural communities planning to and currently implementing evidence-based interventions to address the opioid epidemic, including the promising approaches described above: naloxone distribution, substance use disorder treatment delivered via telehealth, hub-and-spoke models, primary care-behavioral health integration, implementation of comprehensive

syringe service programs, and coordinated prenatal care and substance use treatment. Programs such as those supported by the National Institutes of Health in its Helping to End Addiction Long-term (HEAL) Initiative [122] are examples of significant investments to help local communities, in rural areas and elsewhere, test implementation of an integrated set of proven interventions.

2. Establishing entry points to treatment in rural service delivery settings less likely to invoke self and community stigma among rural populations, such as churches, libraries, and other community-based settings.
3. Providing incentives for waived physicians who work in rural communities to see as many patients in need of medication for opioid use disorder that their license allows. For example, the Blue Care Network in Michigan offers providers a financial incentive for obtaining a DATA 2000 waiver and an additional incentive for each patient who starts treatment with medication for opioid use disorder [16].
4. Providing incentives for providers of non-pharmacologic, non-opioid pain management therapies to operate in rural communities, giving residents an alternative to opioid therapy for pain management.
5. Providing incentives for health care professionals experienced in addiction medicine, behavioral health specialists, social workers, and all health professionals that could contribute to the care of an individual with opioid use disorder to operate in rural communities to address the dearth of providers.
6. Expanding reimbursement for the use of telemedicine to include waived physicians and for providers of non-pharmacologic, non-opioid pain management therapies to reach and serve rural communities.

Veterans

The Importance of Veterans

The prevalence of OUD among Veterans Health Administration (VA)-treated veterans is almost seven times that of the commercially insured [10], making veterans a population of special interest and in special need. Veterans are more likely than the general population to have risk factors for OUD and overdose. For

example, chronic pain is more common and more severe in veterans than in non-veterans, affecting about half of veterans in VA care [63,119]. Among veterans, pain is often complicated by high rates of mental illness, including SUDs, which increases the risk of misusing opioids to treat pain, depression, and serious mental illness [125,131]. As opioid prescribing rose in VA health care, opioid overdoses also increased. Veterans treated in the VA were almost twice as likely to die by overdose as the general population [17]. Among service members returning from the conflicts in Iraq and Afghanistan, there has been concern about misuse of prescription opioids initiated to treat service-related injuries [77]. Even among non-deployed active duty service members, prescription drug misuse almost tripled from 2005 to 2008 [21]. In those being treated by the VA between 2003 and 2010, OUD diagnoses increased by 45% [126].

Barriers to Treatment for Veterans

Veterans experience many of the same barriers to OUD treatment as the general population. For example, stigma is a driver of many barriers to OUD care, including at the system-level (e.g. lack of insurance coverage, laws restricting sharing of information about OUD treatment), provider-level (e.g. lack of motivation and knowledge about how to treat OUD), and patient-level (e.g. lack of awareness about effective treatment) [120,127]. Veterans face geographic challenges in that major facilities for SUD treatment may not be close to where they live, so they must travel long distances to receive treatment. Furthermore, although buprenorphine and injectable naltrexone are on the VA formulary and despite evidence that many patients with OUD can be managed in primary care, facility policies delineating buprenorphine prescribing for OUD as a special clinical privilege often restrict qualified providers from prescribing buprenorphine outside of SUD programs [179]. Fortunately, those treated in the VA system also benefit from unique aspects of the VA health system. SUD treatment is part of the medical benefits of every enrolled veteran and VA SUD treatment programs must offer OUD medication (at a minimum, either buprenorphine or methadone) and treatment of co-occurring mental conditions [163,164]. Buprenorphine/naloxone and extended-release injectable naltrexone are on the VA national formulary for use without any prior authorizations. In addition, as the nation's largest integrated health care system, SUD treatment program information is shared with other VA clinicians. The size

of the VA health care system allows for the systematic development and testing of prevention and treatment approaches that could be adopted by other health care systems.

Promising Approaches

In addition to its national policies facilitating OUD treatment, the VA has implemented multiple strategies to address the opioid epidemic by focusing on OUD prevention through safer pain management and on improved access to OUD treatment. Receipt of opioid pain medication by VA-treated veterans peaked at 21.2% in 2012 and declined annually to 16.7% by 2016 [72]. By leveraging electronic health record data, the VA has developed decision-support tools such as the Stratification Tool for Opioid Risk Mitigation (STORM) to assist clinicians in identifying veterans at risk of opioid-related adverse events, implementing risk-mitigation strategies like urine drug testing and naloxone prescribing, offering non-opioid pain management options like exercise, and offering medication for OUD [113].

The Medication Addiction Treatment in VA initiative provides education to VA providers across the country, and the Psychotropic Drug Safety initiative provides informatics tools and leadership consultation to improve the safety and effectiveness of OUD medication. The Overdose Education and Naloxone Distribution Program provides overdose education and naloxone prescriptions to providers, patients, and their families. According to VA internal medication dispensing data as of November 2019, VA had dispensed over 200,000 naloxone prescriptions [162].

Academic Detailing (AD) is a scholarly approach to balanced, evidence-based information that uses direct one-on-one social marketing techniques to provide a service-oriented outreach for health care professionals [168]. For example, VA facilities implementing AD had a 5-fold higher rate of naloxone prescribing than those without AD [18]. AD has resulted in a dramatic decrease in opioid prescribing, inappropriate benzodiazepine prescribing, and opioid and benzodiazepine combination prescribing [19,133].

The VA Quality Enhancement Research Initiative funds initiatives to increase OUD medication treatment [160]. For example, the Stepped Care for OUD Train-the-Trainer (SCOUTT) initiative trained 18 pilot teams to provide OUD medication for patients in primary care, mental health, and pain clinics. In its first nine months, there was a 107% increase in the number of

patients receiving buprenorphine and a 68% increase in qualified prescribers in its pilot clinics.

These combined efforts have increased the proportion of veterans treated for OUD from 27% in 2010 to over 39% in June 2019 [164]. While this compares favorably to access to OUD treatment in the U.S., substantial variation in treatment rates by facility remains [179].

Research and Action Priorities for Veterans

The VA has made great progress in reducing reliance on opioids and in promoting safer, better pain care. Further research is needed to determine whether these efforts have yielded the expected benefits in terms of longevity, function, quality of life, and prevention of OUD among veterans enrolled in the VA.

The VA has been promoting evidence-based medication treatment for OUD through policy and implementation science for more than 12 years and has made tremendous progress in providing OUD medication in all VA medical centers. However, as in the general U.S. population, the majority of veterans clinically diagnosed with OUD and being treated within the VA are not receiving indicated medications [120,179]. Continued collaboration across the VA is needed to sustain and spread OUD care to all veterans in need in the clinical settings that they prefer, such as primary care, pain clinics, and general mental health clinics. VA facilities could benefit from support for modest additional resources for chronic OUD disease management in primary care and mental health clinics, and from support for provider and patient education about OUD. To reach veterans living in rural areas, the VA may benefit from expanding telehealth programs, community care, and other initiatives to bring OUD care to veterans in rural areas.

Sustained support and expansion of SCOUTT would facilitate chronic disease management of OUD. Development of more effective provider education like simulation learning and electronic health record tools would facilitate evidence-based OUD care. Initiation of OUD treatment in the emergency department and during hospitalization may improve the safety of care transitions and reduce costs associated with OUD.

Examples of specific research and action priorities could include:

1. Expanding access to and improving processes for the administration of medication for opioid use disorder for veterans in primary care settings.
2. Strengthening collaborations between the Department of Defense and the Veterans Health

Administration to improve opioid use disorder prevention and treatment for transitioning veterans, particularly those with service-related painful conditions.

3. Piloting telehealth programs that can reach veterans in rural areas. The VA has had success with these sorts of pilot programs and their learnings could be leveraged to support non-veteran rural populations.
4. Advancing interactive and effective provider education tools to improve evidence-based opioid use disorder care delivery

Adolescents and Young Adults

The Importance of Adolescents and Young Adults

Adolescents and young adults, defined as ages 12–24 for purposes of this manuscript, are at a critical at-risk stage for substance use and require special attention when viewed through the lens of the opioid epidemic. This is due to the developmental tasks of the adolescent and young adult periods, increased vulnerability to use opioids, and unique challenges that this phase of development presents to the prevention and treatment of OUD.

Brain development is not complete until early adulthood, around age 25 [61]. Adolescent brains are highly optimized for learning, in that they create new connections between synapses faster and more efficiently than adults [80]. However, this plasticity makes adolescents more vulnerable to the effects of substance use and increases the risk of developing substance use disorders more quickly than older individuals [101]. In addition to physiologic vulnerability, executive control, judgment, empathy, and insight skills are still being developed in adolescence [80]. Premature developmental skills in young people can enable emotion-based decisions about substance use and increase sensitivity to cultural messaging about the perceived safety of substances such as prescription medications [101]. Adolescents' increased propensity toward risk-taking behavior, while developmentally appropriate to prepare young people for adulthood, can also manifest as an increased proclivity to start opioid use and a reluctance to seek treatment from traditional providers [173].

Adolescents and young adults are, generally, more likely to try opioids than older populations, and when they do initiate use, are more likely to develop an OUD [182]. The 2017 Youth Risk Behavior Survey indicates 14% of high school students have engaged in opioid misuse [89]. Rates of OUD increased nearly six-fold

among the U.S. population under age 25 between 2001 and 2014 [71]. Opioid-related mortality among adolescents aged 15 to 19 increased from 1.6 per 100,000 in 1999 to 3.7 per 100,000 in 2015 [50]. Since 2016, average days supplied of opioid prescriptions written for adolescents have declined, but opioids diverted from family members and friends remain a major source for misuse among adolescents [150]. Adolescents whose family members have an opioid prescription have a 40% increased chance of developing OUD, compared to adolescents without a family member with an opioid prescription [3]. Prescription opioid misuse by adolescents is associated with other substance use, violence victimization, sexual risk-taking, suicidal thoughts and behaviors, and poor academic performance, as well as an increased risk of adverse outcomes such as misuse of opioids and development of OUD in later years [40,110]. Approximately 74% of individuals between the ages of 18 to 30 receiving substance use disorder treatment reported their age of initiation to be 17 or under [152].

Barriers to Treatment for Adolescents and Young Adults

Seeking and accessing treatment for SUD, including OUD, can be challenging in adolescence. Wu, Zhu, and Swartz [178] found that adolescents especially underutilized treatment for OUD. According to the 2015–2017 National Survey on Drug Use and Health (NSDUH), only 27% of all individuals between the ages of 12 and 24 with an OUD reported receiving some SUD treatment in the past 12 months, and only 12% reported perceiving a need for treatment or counseling for their OUD during the past 12 months. This is consistent with previous literature findings on perceived need for treatment to be very low among individuals with an SUD, while also being an important predictor of SUD treatment utilization [2]. Among adolescents reporting a perceived need for SUD treatment but not getting it, the 2015–2017 NSDUH finds affordability to be the primary reason for not getting treatment (47%), followed by lack of readiness to stop using (31%), stigma (27%), lack of treatment access (21%), and treatment not being a priority (10%). To facilitate perceptions of treatment need and eventual treatment utilization, programs and policies could be developed to elevate public perceptions of the benefits of treatment, especially if they are designed to address adolescents and young adults [2].

Another barrier to SUD treatment among adolescents and young adults [12] is the perceived ap-

proachability and confidentiality of family members and health care providers. Adolescents are particularly concerned about the potential repercussions of disclosing substance use if they believe that they would be judged or punished for doing so by their parents [12]. In addition, adolescents can be reluctant to disclose substance use issues to health care providers such as their primary care doctor or school counselors for fear that the information might be disclosed to their parents without their consent [12]. Co-occurring mental health disorders, which are highly prevalent among individuals with OUD, can be both an underlying reason for substance use/misuse and a barrier to seeking treatment. Although national level statistics on co-occurring mental health disorder and OUD for adolescents are lacking, the literature suggests that the rate of co-occurring disorders among adolescents is likely quite high; as such, comprehensive integrated treatment programs appear to be the most effective method of treatment [92]. Furthermore, there is inadequate capacity for both addiction treatment and mental health treatment for this population.

Promising Approaches

There are examples of promising treatment strategies for adolescents with OUD. Medications approved by the U.S. Food and Drug Administration (FDA) for adults with OUD—naltrexone, buprenorphine, and methadone—have not been well studied in adolescents, but the limited evidence available suggests that they would be effective in this population, especially when paired with behavioral therapy, but also if behavioral therapy is not available [120]. Research has shown that outpatient treatment with naltrexone/buprenorphine is associated with long-term engagement with treatment programs and high rates of opioid abstinence [108]. Despite the existence of evidence showing efficacy in adolescents, naltrexone is only approved for individuals 18 and older, buprenorphine is approved for individuals 16 and older, and providing methadone for those under 18 is restricted under federal regulations. In 2016, the American Academy of Pediatrics recommended that pediatricians consider offering MOUD to adolescents and young adults with OUD [44]. However, only 1% of providers with waivers to prescribe buprenorphine are pediatricians [137]. It is especially important to integrate behavioral health care with primary care for adolescents. Regular screening for OUD and related risk factors, including alcohol and cannabis use at an early age, as part of yearly checkups normalizes questions about substance use and can help re-

duce stigma, and a pediatrician prescribing MOUD in their general office can improve access to treatment [101].

OUD treatment for adolescents should also include specific efforts to engage the family and recognize the role that peers play during this developmental stage and the importance of relationships and connectedness to adolescent receptivity to treatment [7,173]. Family involvement in treatment can be critical to the success of an adolescent [7]. Programs for youth should address the developmentally appropriate tasks of adolescents, such as the growing drive for independence that can create conflict within the family [101]. Outreach to and engagement of youth may also require different strategies, such as going into schools, community centers, or other places where adolescents are likely to be rather than relying upon them to come into an office for treatment; providing consistent reminders of appointments by phone or text; providing assistance with transportation; and offering snacks or other comforts in the treatment location [7]. Social media has been shown to have some effect on changing knowledge and attitudes among adolescents and young adults regarding health education, but its effect on behavior change is weak [85]; further research could seek to determine the effectiveness of social media messages in decreasing initiation of opioids and increasing treatment-seeking behavior among adolescents and young adults.

Adolescents and young adults are a population among which early intervention and prevention efforts could result in major changes in terms of development of OUD and its negative impacts. There are a number of ways in which to intervene early, including:

1. Treating co-occurring mental health disorders that often present alongside OUD or SUD;
2. Reducing the risk of initiating substance misuse at an early age through effective and data-driven prevention approaches;
3. Reducing sources of opioids that adolescents or young adults could divert to inappropriate use;
4. Addressing the stigma surrounding SUD/OUD and SUD treatment;
5. Improving appropriate levels of opioid prescribing by health care providers; and
6. Improving financial resources to obtain evidence-based treatment (MOUD) and increasing the availability of MOUD and providers for adolescents.

Many of these approaches are addressed in other sections of this paper, although all approaches will need to be adapted to fit the specific and individual needs of the adolescent and young adult population. Each of these approaches may significantly reduce the onset of SUD/OUD in adolescents and young adults, as well as reduce the negative impacts of such. However, most of these approaches lack a sufficient evidence base and will need additional research into the evidence base and subsequent implementation.

Given the unique challenges posed by adolescence and young adulthood, treating co-occurring mental health disorders, reducing the risk of initiating misuse at an early age, reducing sources of diverted opioids, addressing stigma surrounding substance use disorder, improving opioid prescribing by health care providers, improving financial resources to obtain evidence-based treatment, and increasing availability of MOUD and providers for adolescents could make an important impact in tackling the opioid epidemic. Research by Manuel et al. [106] indicates that a service system designed for an adolescent and young adult population would allow the young person to drive treatment and recovery by being involved in decision-making; train providers about the unique needs of the youth and young adult population; highlight the importance of caring relationships with adults; engage families in treatment with youth and young adults, while acknowledging the developmental need for autonomy; utilize peers, particularly those with lived experience as “transition navigators”; and consider activities such as future planning and life skills development as part of the treatment plan.

Moving upstream from treatment to prevention is also critical. Substance use is “arguably the most important modifiable health risk behavior impacting adolescents” [101]. Clayton et al. [40] indicate that evidence-based health education programs that promote adolescent connectedness (i.e., a sense of caring, support, and belonging to family and school), teach coping and problem-solving skills, and enhance identification, support, and treatment for youth who are most at risk are key primary prevention strategies that can lead to a reduction in substance use among youth. The success rates of these initiatives among this population are promising.

Research and Action Priorities for Adolescents and Young Adults

Examples of specific research and action priorities could include:

1. Consistent with recommendations by the American Academy of Pediatrics [4], training pediatric providers to treat and prevent substance use. In addition, all pediatric residency programs should include training in prescribing medication for opioid use disorder, leading to an increase in the number of pediatricians with waivers to prescribe medication for opioid use disorder for adolescents [4]. These trainings should be supplemented by research on best practices in engaging adolescents with treatment, as these approaches may not be the same as those that are effective for adults.
2. Strengthening general behavioral health training (e.g., including identifying and treating anxiety and depression) and training in substance use disorders and pharmacotherapies for alcohol and opioid use disorders for providers.
3. Addressing the cost of treatment, including insurance coverage for mental health and substance use disorders, for the adolescent and young adult population.
4. Developing adolescent and young adult treatment systems that recognize the unique developmental stage, strengths, and challenges of the population.
5. Promoting research on prevention strategies that incorporate adolescent peers, family members, and schools.

People Who Inject Drugs

The Importance of People Who Inject Drugs

Individuals who inject drugs are at a higher risk for opioid injection drug use-related infectious diseases, as evidenced by localized outbreaks of HIV [49], stabilization of HIV diagnoses since 2010 for nonurban and since 2012 for urban whites who inject drugs after persistent declines over the prior decade [167], and a decade of rising rates of HCV infections [154]. In addition, studies have documented increasing rates of bacterial and fungal infections associated with opioid and other drug injection [136].

Injection drug use is one of the major mechanisms that transmits blood-borne infectious diseases such as HIV, viral hepatitis, and skin and soft tissue infections and infectious endocarditis [136]. In the U.S., HCV infections are primarily transmitted through injection drug use [33], with a seroprevalence above 50% among people who inject drugs [8]. In addition, approximately

6% of people who received an HIV diagnosis in 2016 had their HIV infection attributed to injection drug use [32]. Contraction of these blood-borne infectious diseases, in each case, can lead to serious negative health outcomes and death.

Beyond infectious disease-related harms, people who inject drugs (PWID) are at increased risk for SUD, drug overdose, and engaging in high-risk sexual behaviors [82]. A recent systematic review estimated that 23% of people who inject drugs in the U.S. had experienced a recent nonfatal overdose and 45% had ever experienced an overdose [43]. Another systematic review found that standardized mortality rates were higher than the general population, with drug overdose being a primary underlying cause of death among people who inject drugs [107].

In addition to focusing attention on the infectious disease risks associated with injection drug use, recent outbreaks of HIV and the continued rise in viral hepatitis have identified populations of people who inject opioids or other drugs that are not being reached by culturally informed, evidence-based interventions such as SSPs, MOUD, and HIV and viral hepatitis prevention and treatment services that can prevent or reduce injection-related harms [81,100].

Barriers to Treatment for People Who Inject Drugs

People who inject drugs commonly experience barriers to care. These barriers exist due to significant stigma and social and structural challenges that limit seeking, accessing, and receiving needed services, including substance use, infectious disease, and harm reduction services [13,81]. A recent study found that 70% of individuals who inject drugs had experienced discrimination because of their injection drug use, and more than 1 in 4 reported that they experienced discrimination weekly or more frequently, with frequent discrimination being associated with increased risk for overdose, injection-related illnesses and diseases, mental health issues, and poor wellbeing [48].

Moreover, people who inject drugs often have lower educational attainment, are more likely to experience homelessness, are more likely to be unemployed, are more likely to be living in poverty, are more likely to be uninsured, and are more likely to lack access to reliable transportation, all further constraining their ability to access needed treatment services [15,86]. Having health insurance, and, more specifically, the type of insurance an individual has, are particularly important barriers to treatment. Being uninsured or having

Medicaid has been associated with a lower likelihood of receiving MOUD. In one study, individuals that were uninsured were 47% less likely to receive MOUD and those with Medicaid were 62% less likely to receive MOUD [27]. A recent study among 17 SSPs in Washington State found that more than 75% of respondents expressed being either somewhat or very interested in getting help for their substance use. However, despite this high level of interest in treatment and high levels of insurance coverage (84.4%), primarily Medicaid (83.4% of those with insurance), only 9.4% of respondents had received MOUD in the past year and 11.5% had received non-medication based treatment in the past year [62]. These findings underscore the all-too-common gap that exists between need and interest in treatment and actually receiving it.

Promising Approaches

Reducing risk for overdose, infectious disease transmission, and other injection-related harms among people who inject drugs requires a comprehensive approach that focuses on:

1. Increasing access to sterile injection equipment and education on safe injection practices, infection prevention strategies, appropriate wound care, and reducing high-risk sexual behaviors;
2. Expanding MOUD treatment and other evidence-based treatment and recovery supports;
3. Increasing HIV testing, counseling, provision of pre-exposure prophylaxis (PrEP), and improving linkage to antiretroviral treatment;
4. Scaling up viral hepatitis testing, linkage to direct-acting antiviral (DAA) treatment for HCV, and vaccination for hepatitis A virus (HAV) and hepatitis B virus (HBV); and
5. Increasing the provision of overdose prevention education and naloxone distribution.

SSPs have been shown to reduce injection-related risk behaviors and to decrease HIV, HCV, and hepatitis B virus (HBV) transmission [147,158,177]. Research has consistently shown that SSPs are most impactful when they provide the full complement of risk reduction services, including distribution of sterile syringes/needles without requiring 1-for-1 exchange and allowing for secondary exchange, distribution of other injection equipment, risk reduction education, infectious disease testing, counseling and linkages to treatment, provision of or linkages to substance use treatment, and overdose education and naloxone distribution

[11,159]. Despite the evidence demonstrating their effectiveness, SSPs have been limited in number, scale, and scope in the U.S. due to persistent legal, policy, political, social, and funding barriers, including long-standing restrictions on the use of federal funds to support SSPs, in particular the purchase of syringes and needles [20]. A common argument against SSPs is that they normalize or increase drug use; studies have shown, however, that people who engage with SSPs do not increase their drug use and are significantly more likely to engage in substance use treatment [60,73]. Implementation of SSPs is particularly needed in rural areas of the U.S. and in the South and Midwest where access to these programs is limited and opioid misuse and related harms are disproportionately high [53,84].

A key strategy to reduce opioid-related morbidity and mortality among people who inject opioids or other drugs is through the expansion of MOUD. MOUD reduces opioid use, opioid-related mortality, and the transmission of infectious diseases [99,120]. Although significant progress has been made to expand MOUD [157], the availability of clinicians and facilities that provide MOUD remains insufficient to meet treatment need [6,84]. This is especially important in areas with limited access to MOUD such as in the Southern U.S. [6,84]. In addition, health system touchpoints, such as when an individual who injects drugs is being assessed or treated for injection-related infectious consequences (e.g., endocarditis, osteomyelitis), provide an additional important and often missed opportunity to screen for and provide MOUD. The implementation of low-barrier buprenorphine treatment, including in SSPs, is a promising approach to engaging with high-risk populations, such as people who inject drugs, which have significant barriers to obtaining treatment through traditional treatment programs [76,169].

The CDC recommends PrEP as one prevention option for adults who inject drugs and are at substantial risk of HIV acquisition [30]. Despite this recommendation, PrEP remains underutilized among people who inject drugs. Studies have documented low rates of awareness about PrEP, but higher rates of interest in taking PrEP when people are aware [145]. Thus, strategies to increase access to PrEP among people who inject drugs must be done in coordination with efforts to raise awareness about indications for PrEP. Among individuals living with HIV, treatment with antiretroviral therapy decreases HIV viral load and thus decreases the likelihood of HIV transmission to others [42]. Yet among people with HIV who also inject drugs, there

are numerous challenges in linking treatment and optimizing treatment. A higher proportion of HIV-positive persons who inject drugs have a detectable viral load compared to those who do not inject drugs (48% versus 35%). In addition, condomless sex, exchange sex, and high-risk sex are all more common among those who inject drugs versus those who do not [51]. To ensure decreased mortality among those who inject drugs, it is necessary to leverage innovative service delivery models to strengthen efforts to test for HIV, provide PrEP to those at substantial risk for acquiring HIV, facilitate sexual risk reduction practices, link HIV-positive persons to care, and optimize care for those individuals [153].

Given high rates of viral hepatitis among people who inject opioids or other drugs, there is a critical need to expand testing among this population so that individuals are aware of their status and can be linked to care when viral hepatitis is diagnosed. Direct-acting antivirals (DAAs) represent a major advancement in curative treatment for HCV, with cure rates reaching greater than 90% [5]. However, PWID face significant barriers to receiving DAAs, such as high costs, insurer cost-containment, and clinical utilization strategies that do not exist for people who do not inject drugs. These barriers are largely due to concerns about re-infection in the setting of ongoing substance use [9], despite recent research indicating low rates of re-infection among people who inject opioids or other drugs, especially among those receiving MOUD [1,67]. In addition to curative treatment for HCV, vaccinations for HAV and HBV have long been available, and expanding vaccination among people who inject drugs can help to further prevent the acquisition and transmission of these forms of viral hepatitis. These treatment and preventative interventions should be expanded, especially among hard-to-reach populations, such as people who inject drugs.

Finally, the increased overdose risk among people who inject opioids and the continued proliferation of highly potent synthetic opioids in the illicit drug supply highlight the importance of access to overdose prevention education and naloxone among this population. In recent years, significant progress to expand access to naloxone has been made due to implementation of state naloxone access laws such as pharmacy standing orders, increased community distribution, and efforts to increase community engagement [69]. However, in 2018, approximately 560,000 naloxone prescriptions were dispensed from U.S. retail pharmacies [69], a small fraction of the more than 10 million people

misusing prescription opioids or using heroin in the U.S. [149]. A key strategy for reducing overdose death among people who inject opioids involves expanding pharmacy-based naloxone distribution, naloxone distribution from SSPs, and other harm reduction and community-based programs among people using opioids and those potentially exposed to opioids through mixing of fentanyl other highly potent synthetic opioids into the illicit drug supply.

Research and Action Priorities for People Who Inject Drugs

Examples of specific research and action priorities could include:

1. Increasing access to sterile injection equipment and education on safe injection practices, infection prevention strategies, and appropriate wound care through the expansion of syringe service programs, especially in high-burden areas.
2. Expanding access to medications for opioid use disorder among people who inject drugs, especially buprenorphine and methadone, which have shown a documented reduction in mortality among people who inject drugs. This could include scaling up low-barrier models and providing medications for opioid use disorder in settings frequented by people who inject drugs such as syringe service programs, emergency departments, and infectious disease services within the health system.
3. Increasing HIV and hepatitis testing, counseling, provision of PrEP, efforts to high-risk sexual behaviors, and improved linkage to antiretroviral treatment to prevent the transmission of HIV and hepatitis. This expansion should occur in general medical settings, harm reduction programs, and substance use disorder treatment programs.
4. Scaling up viral hepatitis testing, linkage to direct-acting antiviral treatment for hepatitis C virus, and vaccination for hepatitis A virus and hepatitis B virus in general medical settings, harm reduction programs, and substance use disorder treatment programs.
5. Increasing access to overdose prevention education and naloxone distribution among people who inject drugs, utilizing multiple avenues for intervention, including harm reduction programs, syringe service programs, emergency de-

partments, the criminal justice system, and community pharmacies, among others. In terms of naloxone distribution, specifically advocate that people who inject drugs leave these environments with naloxone in hand, rather than a prescription. It has been documented that individuals do not always fill a naloxone prescription, so having the naloxone in hand will further protect people who inject drugs.

6. Expanding research to identify innovative service delivery models that can increase provision of medications for opioid use disorder and naloxone, increase access to infectious disease testing and treatment, and increase retention in treatment among people who inject drugs.

Conclusion

Despite the considerable resources already allocated to combat the opioid crisis, as well as the progress made in this effort, this review identifies several areas in which additional efforts are needed to best care for populations that have been disproportionately impacted by the opioid crisis.

The most obvious research recommendation and priority area that cuts across all of the special populations is the need for easier access to and broader availability of MOUD. Every special population, and by association all individuals with OUD, would have better health outcomes if they had consistent and affordable access to MOUD. Ensuring this access would make a large and immediate difference in health outcomes for each of these special populations.

Associated with provision of MOUD, all the special populations also note that continuity of care is critical. Many of these populations experience challenges in maintaining treatment, whether it be due to incarceration status or location, distance from provider, or other challenges that may disrupt treatment. Ensuring that individuals who need treatment stay enrolled is another critical aspect of ensuring the best health outcomes for these populations. Telehealth options may be important in ensuring continuity, or in the case of rural populations, initiation of care.

Lack of workforce capacity, belief in treatment solutions, insurance, low motivation and stigma are important barriers to treatment and long-term recovery in these populations. There are also important gaps in knowledge, such as the comparative effectiveness of the three FDA-approved medications for the treatment of OUD or how to select behavioral therapies to be used with these medications.

At the same time, the review identifies some promising practices such as increased use of systematic screening for opioid misuse and OUD and use of more flexible delivery systems (e.g., hub-and-spoke or stepped-care models and telehealth or integration of addiction medicine along with behavioral health and HIV/hepatitis expertise). One area that has received limited attention to date is prevention, despite the fact that less than 50% of individuals with OUD seek treatment. The recently-funded NIH HEAL Prevention initiative and the CDC Overdose Data to Action program may start to address this gap and generate evidence-based interventions that can be implemented in these and other communities.

As we continue to combat the opioid crisis, there is a clear need to develop interventions that are evidence-based but can also be flexibly adapted to the needs, preferences, and resources of each population to ensure that the promise of precision medicine includes not only molecular-based therapies, but also population-oriented approaches. Caring for those who are most impacted by the opioid epidemic is our duty, and therefore developing approaches that will allow us to care for them in the best and most effective ways is critical to ensuring better health outcomes for these populations.

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Box 1 | Research and Action Priorities for Special Populations - Summary

Justice-Involved Populations

1. Initiating and continuing medications for opioid use disorder while individuals are detained or incarcerated, including through the use of telemedicine, and ensuring that medication for opioid use disorder is not interrupted when the individual returns to the community.
2. Supporting the prescription of buprenorphine and methadone (agonist therapies) over naltrexone (antagonist therapy), absent well-designed comparative effectiveness trials that provide evidence of equivalent or better outcomes with naltrexone, and improving education efforts on these therapies to reduce stigma.
3. Pursuing regulatory adjustments that would allow for suspension, rather than termination, of Medicaid when an individual enters a jail or prison, and supporting pilot projects to work with Medicaid Managed Care organizations to facilitate continuity of treatment.
4. Addressing logistical barriers to providing care by, for example, ensuring appropriate numbers of staff with buprenorphine waivers to care for the entire incarcerated population, and addressing regulatory barriers that stand in the way of establishing jail-based methadone treatment programs so that individuals do not need to leave the jail to receive medications for opioid use disorder.
5. Expanding drug court models to require both provision of medications for opioid use disorder and additional social services, and focusing research on establishing standards for consistency and quality between drug courts.
6. Partnering with community organizations to provide employment opportunities for those transitioning out of incarceration and on medications for opioid use disorder, as stable employment has been shown to lead to better overall outcomes.
7. Providing naloxone and naloxone education when an individual is released from incarceration to prevent against accidental death due to overdose.
8. Pursuing legal and regulatory changes that would reduce total and overall incarceration duration for people with opioid use disorder who have not been charged with violent or other serious offenses.
9. Ensuring that individuals who receive treatment for addiction in justice-involved settings also receive care and support for other needs, including health care and mental health needs.

Rural Populations

1. Continuing financial and technical assistance support for rural communities planning to and currently implementing evidence-based interventions to address the opioid epidemic, including the promising approaches described above: naloxone distribution, substance use disorder treatment delivered via telehealth, hub-and-spoke models, primary care-behavioral health integration, implementation of comprehensive syringe service programs, and coordinated prenatal care and substance use treatment. Programs such as those supported by the National Institutes of Health in its Helping to End Addiction Long-term (HEAL) Initiative [122] are examples of significant investments to help local communities, in rural areas and elsewhere, test implementation of an integrated set of proven interventions.
2. Establishing entry points to treatment in rural service delivery settings less likely to invoke self and community stigma among rural populations, such as churches, libraries, and other community-based settings.
3. Providing incentives for waived physicians who work in rural communities to see as many patients in need of medication for opioid use disorder that their license allows. For example, the Blue Care Network in Michigan offers providers a financial incentive for ob-

taining a DATA 2000 waiver and an additional incentive for each patient who starts treatment with medication for opioid use disorder [16].

4. Providing incentives for providers of non-pharmacologic, non-opioid pain management therapies to operate in rural communities, giving residents an alternative to opioid therapy for pain management.
5. Providing incentives for health care professionals experienced in addiction medicine, behavioral health specialists, social workers, and all health professionals that could contribute to the care of an individual with opioid use disorder to operate in rural communities to address the dearth of providers.
6. Expanding reimbursement for the use of telemedicine to include waived physicians and for providers of non-pharmacologic, non-opioid pain management therapies to reach and serve rural communities.

Veterans

1. Expanding access to and improving processes for the administration of medication for opioid use disorder for veterans in primary care settings.
2. Strengthening collaborations between the Department of Defense and the Veterans Health Administration to improve opioid use disorder prevention and treatment for transitioning veterans, particularly those with service-related painful conditions.
3. Piloting telehealth programs that can reach veterans in rural areas. The VA has had success with these sorts of pilot programs and their learnings could be leveraged to support non-veteran rural populations.
4. Advancing interactive and effective provider education tools to improve evidence-based opioid use disorder care delivery

Adolescents and Young Adults

1. Consistent with recommendations by the American Academy of Pediatrics [4], training pediatric providers to treat and prevent substance use. In addition, all pediatric residency programs should include training in prescribing medication for opioid use disorder, leading to an increase in the number of pediatricians with waivers to prescribe medication for opioid use disorder for adolescents [4]. These trainings should be supplemented by research on best practices in engaging adolescents with treatment, as these approaches may not be the same as those that are effective for adults.
2. Strengthening general behavioral health training (e.g., including identifying and treating anxiety and depression) and training in substance use disorders and pharmacotherapies for alcohol and opioid use disorders for providers.
3. Addressing the cost of treatment, including insurance coverage for mental health and substance use disorders, for the adolescent and young adult population.
4. Developing adolescent and young adult treatment systems that recognize the unique developmental stage, strengths, and challenges of the population.
5. Promoting research on prevention strategies that incorporate adolescent peers, family members, and schools.

People Who Inject Drugs

1. Increasing access to sterile injection equipment and education on safe injection practices, infection prevention strategies, and appropriate wound care through the expansion of syringe service programs, especially in high-burden areas.

2. Expanding access to medications for opioid use disorder among people who inject drugs, especially buprenorphine and methadone, which have shown a documented reduction in mortality among people who inject drugs. This could include scaling up low-barrier models and providing medications for opioid use disorder in settings frequented by people who inject drugs such as syringe service programs, emergency departments, and infectious disease services within the health system.
3. Increasing HIV and hepatitis testing, counseling, provision of PrEP, efforts to high-risk sexual behaviors, and improved linkage to antiretroviral treatment to prevent the transmission of HIV and hepatitis. This expansion should occur in general medical settings, harm reduction programs, and substance use disorder treatment programs.
4. Scaling up viral hepatitis testing, linkage to direct-acting antiviral treatment for hepatitis C virus, and vaccination for hepatitis A virus and hepatitis B virus in general medical settings, harm reduction programs, and substance use disorder treatment programs.
5. Increasing access to overdose prevention education and naloxone distribution among people who inject drugs, utilizing multiple avenues for intervention, including harm reduction programs, syringe service programs, emergency departments, the criminal justice system, and community pharmacies, among others. In terms of naloxone distribution, specifically advocate that people who inject drugs leave these environments with naloxone in hand, rather than a prescription. It has been documented that individuals do not always fill a naloxone prescription, so having the naloxone in hand will further protect people who inject drugs.
6. Expanding research to identify innovative service delivery models that can increase provision of medications for opioid use disorder and naloxone, increase access to infectious disease testing and treatment, and increase retention in treatment among people who inject drugs.

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