

Empirical Studies Addressing the Opioid Epidemic: An Urgent Call for Research

Gregory L Stuart¹, Ryan C Shorey², Christopher R France³, Jenny Macfie¹, Kathryn Bell⁴, Kimberly B Fortner⁵, Craig V Towers⁵, Paul Schkolnik⁶ and Susan Ramsey⁷

¹Department of Psychology, The University of Tennessee-Knoxville, Knoxville, TN, USA.

²Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI, USA.

³Department of Psychology, Ohio University, Athens, OH, USA. ⁴Department of Psychology, Capital University, Columbus, OH, USA. ⁵The Department of Obstetrics and Gynecology, University of Tennessee Medical Center, Knoxville, TN, USA. ⁶Maryhaven, Inc., Columbus, OH, USA. ⁷Departments of Psychiatry & Human Behavior and Medicine, The Warren Alpert Medical School of Brown University, and Rhode Island Hospital, Providence, RI, USA.

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ABSTRACT: Opioid misuse has become one of the most pressing public health problems facing the country. In this article, we briefly review literature regarding the opioid epidemic in the United States and the negative consequences of opioid use disorder. We provide information regarding treatment and relapse using a variety of intervention approaches. We call for research on people with opioid use disorder that can contribute to a variety of areas: improving medication-assisted treatment, addressing chronic pain, examination of adjunctive behavioral interventions, overdose, high risk behaviors and infections, pregnancy, diverse populations, and other psychological factors. Collectively addressing these crucial areas of research will advance the field and help alleviate suffering and prevent death from opioid use disorder.

KEYWORDS: Opioid epidemic, medication-assisted treatment, opioid use disorder, overdose, pregnancy

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CORRESPONDING AUTHOR: Gregory L Stuart, Department of Psychology, University of Tennessee-Knoxville, 1404 Circle Drive, Knoxville, TN 37996, USA. Email: gstuart@utk.edu

It is clear that the United States is in the midst of a serious opioid epidemic and that addressing this crisis is a national health priority.¹ Indeed, some have even called the current epidemic the worst in the history of the United States,² with an estimated 92 million American adults reporting the use of prescription opioids in 2015.³ Approximately 2.4 million people have an opioid use disorder either due to prescription opioid use or heroin use in the United States.⁴ From 1999 to 2015, the number of deaths due to opioid-involved overdoses has quadrupled, with more than 33 000 deaths in 2015,⁵ a number that is expected to increase. Estimates suggest that 91 people die each day in the United States from an opioid overdose,⁶ and approximately 1000 people are treated in emergency departments daily due to opioid use.⁷ Moreover, opioid misuse is associated with increased risk for contracting human immunodeficiency virus (HIV)⁸ and hepatitis C.⁹ Finally, it has been estimated that the opioid epidemic costs the United States approximately US \$78 billion annually.^{10,11}

Opioid use disorder has been described as a chronic, difficult to treat, and relapsing condition.^{12,13} Approximately 60% of patients with an opioid use disorder relapse following inpatient psychological treatment.¹⁴ Similarly, most of the patients treated with methadone relapse following treatment.¹⁵ Although there has been wide variability in relapse and abstinence rates across intervention studies, it is crucial to identify means of improving treatment outcomes for individuals with opioid use disorder.¹⁶ Identifying key factors with respect to

readiness to change and sustaining long-term change will be critical to address this issue.

In light of the extremely high prevalence of opioid use disorder, the enormity of negative consequences associated with it, and the disappointing results of psychological and pharmacological treatments, *Substance Abuse: Research and Treatment* seeks manuscript submissions that address the cause, course, prevention, or treatment of opioid misuse and opioid use disorder. Specific areas of importance for research are described below.

Improving Medication-Assisted Treatment for Opioid Use Disorder

Medication-assisted treatment has quickly emerged as a first-line treatment for opioid misuse and opioid use disorder.¹⁷ Three common medications used in the United States to treat opioid use disorder are methadone, buprenorphine/naloxone, and naltrexone.

Methadone has been the most commonly used type of opioid replacement therapy.¹⁶ Methadone is associated with improved quality of life, increased rates of treatment retention, and lower illicit drug use and HIV risk behaviors.¹⁸ Nonetheless, relapse remains a huge problem for individuals in methadone maintenance therapy, with relapse rates ranging from 20% to 70%.¹⁶

Buprenorphine, a partial opioid agonist, has rapidly expanded the treatment of opioid use disorder in the United States¹⁹ with some promising results. For instance, buprenorphine reduces opioid use and increases retention compared



with placebo,²⁰ and opioid-related emergency department visits and mortality risk associated with illicit opioid use have decreased in buprenorphine patients.^{21,22} Relative to methadone, individuals taking buprenorphine are less likely to overdose^{18,21} and experience respiratory depression. Nonetheless, almost two-thirds of patients discontinue buprenorphine treatment within 6 months, and retention in buprenorphine treatment is poor.^{23,24} Finally, relapse rates among individuals in buprenorphine treatment typically range from 50% to 90%.²⁵

Naltrexone is an opioid antagonist that decreases or prevents the positive effects of opioids and is available in pill, implant, and injectable forms. Despite randomized controlled trials showing some promise for naltrexone, naltrexone is often underused in treatment settings due to lack of patient acceptance.¹⁴ Similar to other medication-assisted treatments, relapse rates remain high (eg, over 80% for oral naltrexone, over 45% for the naltrexone implant, and over 40% for injectable naltrexone).^{26,27} In addition, patients enrolled in the clinical trials often do not complete the full protocol or obtain a full dose of treatment.²⁸ Furthermore, the risk of overdose is high for people during the course of and subsequent to naltrexone treatment.²⁸

Thus, treatment outcome results from studies of all forms of medication-assisted therapies to date remain unacceptably poor. *Substance Abuse: Research and Treatment* calls for research that explores ways of improving medication-assisted treatment outcomes for opioid use disorder.

Addressing Chronic Pain in Patients with Opioid Use Disorder

A complicating factor when treating opioid use disorder is the high level of chronic pain evidenced in this population. For example, among those who misuse opioid medications, nearly two-thirds report doing so to obtain relief from physical pain.³ Up to 60% of patients entering medication-assisted treatment for opioid use have chronic pain conditions,²⁹ and the presence of comorbid pain is associated with poorer opioid treatment outcomes.³⁰ Moreover, approximately 50% of patients receiving opioids for chronic back pain report a lifetime history of opioid use disorder,³¹ and studies have suggested that this rate may be as high as 70% for individuals seeking treatment for other pain conditions.³² Therefore, researchers and clinicians must find better ways to treat pain in an effort to (1) reduce the need for opioids among those with acute or chronic pain, (2) prevent misuse when there is a need for opioid medication, and (3) improve treatment outcomes among those with chronic pain who develop opioid use disorder. Manuscripts examining these issues would be welcome in *Substance Abuse: Research and Treatment*.

Adjunctive Behavioral Interventions with Medication-Assisted Treatment

Adjunctive behavioral interventions for people receiving medication-assisted treatment have been proposed as a way to improve treatment retention, adherence, and outcomes.^{33,34} Much of existing research has centered around adjunctive

behavioral interventions for individuals receiving methadone treatment, with less known about the impact of these adjunctive behavioral interventions on other forms of medication-assisted treatment.¹⁴ Unfortunately, a recent review of some adjunctive behavioral interventions for patients receiving buprenorphine demonstrated little evidence of benefit.³³ There is a pressing need for research that examines new adjunctive, empirically supported interventions for patients in medication-assisted treatment. Such interventions could target cravings, comorbid psychiatric conditions (including affective disorders and post-traumatic stress disorder), and pain, as cravings, comorbid psychiatric conditions, and pain are associated with treatment attrition and relapse.^{35–39} Mindfulness-based interventions^{32,40} and related treatments such as acceptance and commitment therapy may be beneficial, as evidence suggests that they may be effective at reducing cravings, depressive relapse, and pain⁴¹ and could improve outcomes for patients with opioid use disorder. Indeed, one study demonstrated the feasibility and acceptability of a 6-week mindfulness-based program for methadone patients.⁴² Future researchers should examine the impact of these, and other, adjunct interventions on treatment adherence and outcomes across different forms of medication-assisted treatment.

Overdose

Opioid-related overdoses, often resulting in fatalities,^{5,6,43} are a growing problem, particularly since the addition of fentanyl and other powerful synthetic opioids to the drug supply in the United States. For 6 states that track fentanyl fatalities, the number of fentanyl-related deaths increased by over 350% between 2013 and 2014, from 392 to over 1400.⁴⁴ *Substance Abuse: Research and Treatment* invites articles that address strategies of preventing opioid misuse and opioid use disorder from occurring in the first place, derived from a better understanding of the factors contributing to the initiation and evolution of this disorder, as well as research that specifically targets prevention of opioid overdose. Expansion of the use, accessibility, and availability of naloxone⁴⁵ could be helpful to prevent overdose-related fatalities. First responders play an essential role in delivering naloxone to those experiencing an opioid-related overdose^{46,47} and connecting these individuals with treatment. Research on methods to enhance first responders' recognition and response to opioid-related overdoses is encouraged. Other efforts could be directed at developing and supplying tools to help those with opioid use disorder to identify the presence of fentanyl and other synthetic opioids prior to injection.

High-Risk Behaviors, Infection, and Opioid Use Disorder

Opioid misuse is associated with increased risk for contracting HIV⁸ and hepatitis C.⁴⁸ *Substance Abuse: Research and Treatment* calls for articles that assess HIV and HIV risk behavior in people with opioid use disorder. Furthermore, persons living with HIV (PLWH) are 40% more likely to be prescribed opioids

compared with uninfected individuals,⁴⁹ and drug overdose is a leading cause of death among PLWH.^{50,51} Hepatitis C has now become the most common blood-borne infection in the United States, and much of this increase is associated with opioid misuse via intravenous and perimucosal transmission routes.^{52,53} Therefore, PLWH may warrant special attention regarding the prevention and treatment of opioid use disorder and overdose.

Opioid Use Disorder in Pregnancy

The prevalence of opioid use in pregnancy has rapidly increased in recent years along with a concomitant increase in neonatal opioid withdrawal syndrome (NOWS) in newborns. The American College of Obstetricians and Gynecologists briefly reviewed the literature, summarized in Committee Opinion No. 711,⁵⁴ and noted that opioid use in pregnant women increased by almost 5 times from 2000 to 2009 and that the incidence of NOWS was 4 times higher in 2013 than it was in 1999.⁵⁴ Given the magnitude of the opioid use epidemic, the National Institutes of Health recently called for research on a variety of topics related to opioid use in pregnancy.⁵⁵ Work needs to be performed to examine optimal ways of conducting detoxification from opioids during or following pregnancy,⁵⁶ ways of maintaining a woman's desired opioid status postpartum, the use of opioid agonist treatment during and following pregnancy, and careful examination of fetal, neonatal, and postnatal outcomes for mother and infant in women on opioid medication-assisted treatment and detoxification. Indeed, there is a tremendous need for studies that compare the maternal, neonatal, and infant outcomes of pregnant women with opioid use disorder who undergo detoxification or medication-assisted treatment to identify the optimal treatment approaches.^{54,56} In addition, it is important to investigate factors that influence NOWS, given that there is no clear relationship between opioid replacement dose during pregnancy and NOWS in newborns.⁵⁴

Research in Diverse Populations

The aforementioned suggestions for future research should be conducted in a large spectrum of diverse populations. Research is critically needed in individuals with racial/ethnic and socioeconomic diversity, among female patients, in LGBTQIA+ communities, and in patients with a wide variety of substance use, medical, and mental health comorbidities.

Psychosocial Factors Associated with Opioid Use Disorder

Opioid misuse is associated with a range of detrimental problems affecting the individual, their social network, and the community, including childhood maltreatment, criminal activity, economic burden, trauma exposure and post-traumatic reactions, and intimate partner violence^{11,57–60} These and other psychosocial factors may affect treatment engagement, treatment attrition, and relapse risk, whereas participation in medication-assisted treatment and adjunctive behavioral interventions may reduce

psychosocial problems associated with opioid misuse.¹⁴ For instance, a study of opioid users in California found that first time engagement in opioid agonist treatment reduced costs of crime in the 6 months following treatment initiation.⁶¹ Further research is essential to better understand how psychosocial factors, including but not limited to childhood maltreatment and trauma, criminal activity, and intimate partner violence, are affected by engagement in medication-assisted treatments and adjunctive behavioral interventions for opioid use disorder and comorbid conditions and how these psychosocial factors might moderate treatment outcomes.

Author Contributions

All authors contributed meaningfully to the concept or design of the work and/or drafted or revised the article, and approved the version to be published.

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