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Substance Use Disorders (FG Moeller, Section Editor)

Risk Factors for Opioid Overdose

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Abstract

Purpose of Review Opioid overdoses have risen starkly over the last two decades in the USA and are now among the leading causes of overall mortality. This review summarizes the current literature on risk factors for overdose as well as public health solutions.
Recent Findings Although opioid overdose mortality is highest among men and non-Hispanic whites, the rate of death is rising more rapidly now among women and non-Hispanic blacks. Incarceration remains a significant risk factor for overdose death, especially in the first weeks upon reentry reflecting the absence of treatment in prisons and jails despite strong evidence for the benefits of pharmacotherapy integration into these settings. Pharmacotherapy with either methadone or buprenorphine greatly reduces the risk of overdose; however, treatment discontinuation leads to an increase risk of death.
Summary Naloxone distribution both through co-prescribing and community-based opioid overdose prevention programs remains the fundament of the public health response. Both are effective and cost-effective in reducing overdose; however, uptake is hampered due to variance in state naloxone access and Good Samaritan laws. Supervised injection facilities are a promising innovation to address overdose, especially in communities with high overdose rates.

Introduction

Opioids are the public health crisis of the twenty-first century in the USA. The opioid crisis is made up of the related epidemics of opioid overprescribing, misuse, addiction, overdose, and overdose death and involves both opioid analgesics and heroin which are increasingly contaminated with synthetic opioids such as fentanyl.

From 1999 through 2012, the age-adjusted drug-poisoning death rate nationwide more than doubled, from 6.1 per 100,000 population in 1999 to 13.1 in 2012. During the same period, the age-adjusted rates for drug-poisoning deaths involving opioid analgesics more than tripled, from 1.4 per 100,000 in 1999 to 5.1 in 2012 [1]. Overdose deaths have continued to increase across all demographic and geographic groups. In 2016, there were over 63,000 drug overdose deaths, two thirds of which involved an opioid and from 2015 to 2016, the greatest overall death rate increase continues to involve opioids, specifically synthetic opioids [2]. More Americans are dying from overdose annually then died at the height of the HIV/AIDS epidemic [3] and higher than the total death rate of Americans during the Vietnam War [4].

Overdose deaths have shifted mortality rates, especially for middle-aged white non-Hispanic Americans. In contrast to Western European countries and Canada, the all-cause mortality for US whites has increased since 2000, an increase driven overwhelmingly by an increase in overdose deaths [5••]. Among individuals aged 50–54, all-cause mortality rates are higher for white non-Hispanics with a high school or less education than those of other racial and ethnic groups [6].

Recently, the quality of overdose death surveillance data, specifically methods used to classify opioid-related deaths in death certificates, has been called into question [7]. Specific substances are not always listed on death reports. Imputation methods have been used to correct mortality rates when no drug was specified. For example, Ruhm calculated an opioid-related death rate that was 24% greater after imputation than reported, a difference that ranged greatly by geographic region [8]. Similarly, enhanced surveillance in Maryland identified almost twice as many heroin overdose-related deaths than captured in standard death certificates [9]. The current overdose epidemic, enormous as it is, may actually be greater than previously described.

In this paper, we will review risk factors for opioid overdose with an emphasis on overdose death. Specifically, we will look at risk factors at the level of the individual (gender, age, and race) as well as examine contextual factors such as post-incarceration and post-treatment that contribute to overdose risk. Finally, we will discuss clinical and public health approaches to reduce the risk of overdose and overdose death, specifically for individuals with opioid use disorder.

Individual-Level Risk Factors

Overdose and especially overdose death are strongly associated with substance use disorder [10•]. Overdose is more common among individuals with opioid as opposed to other substance use disorder and appears to be higher among individuals who use both prescription opioids and heroin and among those who inject drugs [11–13]. Overdose deaths are often associated with other substance use, specifically alcohol, benzodiazepines, or cocaine [14–17]. For individuals prescribed opioids for pain, the risk of opioid overdose death increases with increases in daily opioid dose [18]. Previous non-fatal overdose is strongly associated with subsequent fatal overdose [19, 20].

Gender

Women are prescribed more opioids than men. Past month opioid use (for years 2007 to 2012) was higher among women (7.2%) than that in men (6.3%) within all age categories, with women aged 60 and over reporting the highest amount of opioid use (8.6%) [21]. However, more men than women die of an opioid overdose, and prescription opioid death rates are higher among men than women [2]. This gap is narrowing as the rate of prescription opioid overdose death is increasing more rapidly for women than for men (471 versus 218% from 1999 to 2015) [22•].

Population health data on gender and overdose risk are somewhat mixed with most studies suggesting that men have a higher risk of overdose than women. A meta-analysis of 29 studies that looked for risk markers for fatal and non-fatal prescription drug overdose identified male sex as one of six risk markers with a summary odds ratio of 1.33 (95% CI 1.17, 1.51) compared to female sex [10•]. These findings, however, are not specific to opioids as only 10 of the 29 included articles focused on prescription opioids.

In contrast, data from a large national cohort of more than 200,000 privately insured US adults with non-cancer pain who filled an opioid prescription indicate that women were more likely than men to overdose. The incidence of drug overdose for women was 0.76%, compared to 0.56% for men, even though the average morphine equivalent daily dose (mg) was higher for men than women (median 40 versus 37.5) [23]. Overall, women in this cohort were younger and more likely to have a co-occurring psychiatric condition. Although women were more likely to be prescribed medications such as antidepressants, benzodiazepines, or zolpidem than men, overdose risk was not gender equal in terms of poly pharmacotherapy. Benzodiazepine use was associated with a higher risk of overdose among men than women, and zolpidem use was a significant risk factor for overdose in women only. These findings partly parallel CDC guidelines that recommended against concurrent use of benzodiazepines and opioids [24••] as well as recent FDA dose recommendations regarding zolpidem for women. In 2013, the Food and Drug Administration reduced the initial recommended dose for zolpidem in women from 10 to 5 mg daily for the immediate release tablet, and from 12.5 to 6.25 mg daily for the controlled release because of the risk of next-morning impairment in women involved in activities that require alertness, such as driving [25].

Age

Age is a commonly cited risk factor for overdose and overdose death. Overall overdose deaths from prescribed opioids increase with age with the highest rates among individuals aged 45 to 54, although the percent change was greatest among those 15 to 24 [2]. Meta-analysis data similarly identified those aged 35 to 54 at greatest overdose risk [10•]. An age period cohort analysis using information from the National Center for Health Statistics' multiple-cause-of-death file for 1999 to 2014 found that baby boomers (individuals born between 1947 and 1964) have experienced the highest mortality from both prescription opioid and heroin overdose [26].

Gender, however, modifies the relationship between age and overdose risk. Older women, aged 65 or greater, have the highest overdose risk [23], an observation supported by recent CDC data [2]. Whereas the age-adjusted rate for prescription opioid overdose deaths increases by each age category for women, it levels off by age for men aged 45 and greater [23].

Race

There has been a great amount of attention to racial differences in opioid prescribing and overdose death in the USA. White race is an oft-cited independent risk factor for opioid overdose and overdose death. This relates, in part, to the fact that white patients are more likely to be prescribed opioids, especially in emergency department settings [27, 28], a disparity that is constant across

socioeconomic status [29] and among children [30]. However, the difference in overdose by race appears to be narrowing as recently overdose rates are increasing more rapidly among blacks.

Out of the 14 studies that examined race as a risk marker, 11 showed that whites were at increased risk for prescription drug overdose as compared to all other racial groups combined, with an overall summary odds ratio of 2.28 (95% CI 1.93, 2.70) [10•]. Although mortality rates remain highest for non-Hispanic whites, mortality is increasing more rapidly for blacks, especially for those aged 45 and older [31]. From 2015 to 2016, blacks have had a 27% increase in age-adjusted overdose death for prescription opioids and a 56% increase for all opioids compared to 9 and 26%, respectively, for whites [2]. Similarly, although hospitalization admissions for both prescription opioid and heroin overdose are higher among whites than blacks, the difference has narrowed between 2001 and 2012 [32].

Contextual Risk Factors

Incarceration and Reentry

Substance-related racial disparities are compounded by inequities in the criminal justice system in the USA [33]. Blacks are incarcerated at a higher rate than other racial groups [34], a disparity that is greatest among drug offenders [35, 36]. This is despite the increased prominence of diversion programs designed to reduce prison entry for those with substance use disorders [37].

Addiction is more common among prisoners than the general population [38], especially among female prisoners [39•], with reported rates as high as 72% among those recently incarcerated [40]. However, few prisoners receive treatment while incarcerated [41, 42, 43•] despite a large evidence base documenting the benefit of providing opioid pharmacotherapy specifically in prison settings [44•, 45].

Prior incarceration is a risk factor for overdose [46] to a large extent because of absent treatment in prisons and poor community-based linkages during reentry. Data from Washington State identified overdose as the leading cause of overall mortality following prison release with a rate of 223 deaths per 100,000 person-years [47], a rate 3.5 times higher than the rest of the state [48]. The rate of overdose mortality was highest within the first 2 weeks of release (3661 per 100,000 person-years) and overall higher among women than men (HR 1.38; 95% CI 1.12, 1.69) [47]. The temporal proximity of overdose death to prison release has also been observed in data from New Mexico where the relative risk of death in the first 2 weeks contrasted with the subsequent 10 weeks was 3.08 (95% CI 1.83, 5.16) [49] and has been observed in data from Canada [50], Australia [51•, 52], the UK [51•, 53, 54], and Norway [55]. Contributing to the elevated overdose risk in newly released inmates is poor social support, financial insecurity, inadequate housing, and drug exposure in their living environments [56].

The evidence clearly points to the public health benefit of providing pharmacotherapy for opioid use disorder in correctional settings [57, 58] and is supported by qualitative research among former inmates [59]. Even in the absence of any specific aftercare for reentry, randomized trial data of methadone pharmacotherapy continuation in jail versus forced withdrawal resulted in an adjusted hazard ratio of 2.04 (95% CI 1.48, 2.80) of engagement in a

community methadone clinic upon release [60]. The provision of pharmacotherapy for opioid use disorder in prison is associated with a decrease in overall mortality [61] and overdose death [62] following release, with the greatest reduction seen in the first 4 weeks, corresponding to the time of the highest overdose risk.

Treatment Discontinuation

There is evidence that discontinuity of opioid use disorder treatment is also a risk factor for overdose. A meta-analysis of 19 cohort studies that followed 122,885 people treated with methadone over 1.3–13.9 years and 15, 831 people treated with buprenorphine over 1.1–4.5 years found that retention in methadone and buprenorphine treatment is associated with substantial reductions in the risk for overall and overdose mortality [63••]. Pooled overdose mortality per 1000 person-years in treatment was 2.6 for methadone and 1.4 for buprenorphine pharmacotherapy and rose to 12.7 and 4.6 respectively for those out of treatment [63••]. The difference between treatment mortality by pharmacotherapy methods may be explained by the relative increase in mortality during methadone, as opposed to buprenorphine, induction [64, 65].

Overall mortality is reduced by 50% during treatment with pharmacotherapy [66] as is overdose death [67], an effect that appears to be moderated by exposure: the longer the treatment, the greater the reduction in mortality [68]. Retention in treatment varies in the literature, although methadone is associated with greater treatment retention than buprenorphine [69•] and buprenorphine discontinuation is primarily involuntary, that is, due to failure to follow strict program requirements [70]. However, mortality is similarly increased with treatment discontinuation as it is with transfer to a different medical setting [71]. Similar to data on mortality following incarceration, the risk of overdose death is highest in the first month after discontinuation of therapy [63••].

Overdose Prevention

Opioid overdose occurs among individuals with opioid use disorder and among individuals on opioid therapy without opioid use disorder. Among patients receiving opioid therapy, the hazard of overdose is twice for long-acting compared to short-acting opioids (HR 2.33; 95% CI 1.26, 4.32) and particularly marked in the first 2 weeks of treatment initiation (HR 5.25; 95% CI 1.88, 14.72) [72]. Hence, current opioid-prescribing guidelines stress utilizing low-dose short-acting medication when opioids are indicated [24••, 73]. In addition, naloxone co-prescribing is recommended for patients on opioid doses greater than 50 morphine milligram equivalents per day or concomitant use of benzodiazepines [24••]. Co-prescribing is acceptable to primary care providers [74] and has been considered a "Universal Precaution" [75], although patients encounter pragmatic barriers, such as cost [76].

Naloxone administration is central to the prevention of opioid overdose death [77] and has emerged as a central public health intervention to reduce one of the risks of opioid use disorder [78]. Lay administration of naloxone either through direct patient prescribing or through

community-based opioid overdose prevention programs is effective in increasing survival from overdose [79, 80]. Additionally, they are cost-effective [81] with an estimated 1 death prevented for every 227 naloxone kits distributed to people who use heroin [82].

There is legislative variance by the US state regarding both lay naloxone access and overdose Good Samaritan laws [83]. Data through 2014 indicate that states with naloxone access laws had a 14% decrease in overdose mortality ($p = 0.033$) and states with Good Samaritan laws had a 15% decrease ($p = 0.050$) [84]. Healthcare providers, however, are neither knowledgeable nor comfortable with community-based opioid overdose prevention efforts [85] and tend to refer patients to such programs who are at low risk of experiencing or witnessing an overdose [86].

Syringe exchange programs are essential to preventing the transmission of HIV and HCV among people who inject drugs and can serve as platforms for naloxone distribution [87] and possibly for fentanyl self-testing [88]. There are, however, no data regarding a direct reduction in overdose from syringe exchange programs. In contrast, overdose mortality can be reduced by supervised injection facilities [89, 90]. For example, overdose mortality decreased by 35% in the neighborhood adjacent to a medically supervised injection facility in the 2 years after opening in Vancouver compared to the 2 years prior [91••]. Although there are no sanctioned supervised injection facilities in the USA to date [92], several municipalities have passed legislation for their establishment, a public health measure with support from both healthcare providers and syringe exchange clients [93].

Interestingly, there is an association between medical cannabis laws and opioids. Both Medicaid and Medicare beneficiaries in states with medical cannabis legislation fill fewer prescription drugs, including opioids [94, 95], and there is some data that cannabinoids enable opioid dose reduction without loss of opioid efficacy [96]. Data regarding medical cannabis and overdose mortality are mixed. Death certificate date demonstrates a decrease in opioid analgesic mortality within states with medical cannabis legislation, an association that has strengthened over time [97], and may be more pronounced with more liberal allowance for dispensaries [98]. CDC WONDER data, however, demonstrate the opposite, an increase in opioid-related mortality among states with medical cannabis laws, although this relationship was modified by state prescription drug monitoring programs [99]. Although liberalization of cannabis may reduce opioid overdose, there is no evidence that legalization of illicit opioids would [100].

Conclusion

Opioid overdoses have risen starkly over the last two decades in the USA and are now among the leading causes of overall mortality. Although opioid overdose mortality is highest among men and non-Hispanic whites, the rate of death is rising more rapidly among women and non-Hispanic blacks. Incarceration remains a significant risk factor for overdose death, especially in the first weeks upon reentry reflecting the absence of treatment in prisons and jails despite strong evidence for the benefits of pharmacotherapy integration into jail settings. Pharmacotherapy with either methadone or buprenorphine greatly

reduces the risk of overdose; however, treatment discontinuation leads to an increase risk of death. Naloxone distribution both through co-prescribing and community-based opioid overdose prevention programs remains the fundament of the public health response. Both are effective and cost-effective in reducing overdose; however, uptake is hampered due to variance in state naloxone access and Good Samaritan laws. Supervised injection facilities are a promising innovation to address overdose, especially in communities with high overdose rates.

Compliance with Ethical Standards

Conflict of Interest

Thokozeni Lipato declares that he has no conflict of interest. Mishka Terplan declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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