MEDICATION-ASSISTED TREATMENT AND OPIOID USE RESPONSE TO OPIOID OVERDOSE SENTINEL EVENTS

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Abstract

Introduction

A nonfatal overdose due to opioids can be viewed as a failure to adequately treat addiction or as an opportunity to start or improve treatment for opioid use disorder (OUD). It is important to determine how patients are being treated before and after an overdose. Primary care providers are at the forefront of the opioid epidemic and have the potential to influence opioid prescribing habits and treatment of OUD. Evaluation of the opioid epidemic leading to potential solutions has significant public health relevance.

Objective

To determine treatment utilization before and after nonfatal overdoses.

Methods

We conducted a longitudinal retrospective cohort study of Pennsylvania Medicaid patients aged 12-64 with a nonfatal opioid or heroin overdose event between 2008-2013. We measured unduplicated patient-level univariate descriptive statistics for demographic and treatment utilization 6 months before and 6 months after an overdose. We identified inpatient, outpatient, and pharmacy claims data from Pennsylvania's managed care and fee-for-service Medicaid programs. We excluded Non-Pennsylvania residents, those dually-eligible for Medicare, age < 12 or age > 64, and non-opioid or non-heroin overdoses for a total of 7,690 enrollees. We evaluated the following demographic factors: age, gender,

and race. The main outcome measure was OUD medication-assisted treatment (MAT) utilization: methadone, buprenorphine, and naltrexone. Secondary outcome measures included the length (days) supply of prescription opioids pre and post-overdose.

Results

Among 3,009 enrollees who had a heroin overdose and 4,989 who had a prescription opioid overdose, most were <40 years old and white. Among those who survived after the non-fatal overdose, opioid use did not change in the heroin group (40.6% pre and 39.7% post, P = 0.12). Whereas enrollees in the opioid group were less likely to fill opioid prescriptions post-overdose (65.4% to 59.6% p < 0.001). Likewise, the percent of enrollees with ≥90 days duration of opioids did not change in the heroin group pre- to post-overdose (9.4% to 9.0%, P =0.07) but decreased in the opioid group (32.2% to 28.3%, P < 0.001). MAT increased after overdose in the heroin (28.7% to 33.0%, P < 0.001) and opioid group (from 13.6% to 15.1%, P = 0.001).

Conclusions

Overall, we saw similar OUD medication and treatment utilization rates before and after overdose events. These findings are concerning because they show a lack of addiction treatment escalation after an overdose.

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Background

Morbidity and mortality due to opioids are one of the biggest public health issues affecting Americans today. In 2015 alone, there were 20,101 overdose deaths related to prescription opioid medications, and 12,990 overdose deaths related to heroin.[1] This represents at 2.8-fold increase in the total number of deaths involving opioids since 2002.[2] The Centers for Disease Control and Prevention (CDC) and The White House have publicly stated that the effects of opioids have reached epidemic proportions.[1,3] There are no boundaries for the crippling reach of opioids, which have impacted every state in the nation and every demographic. Rates of opioid overdose deaths are also on the rise globally, which has raised concerns about a potential worldwide opioid pandemic.[4] This epidemic has been building for decades and it will take a coordinated systems approach to change the course of the crisis.

Opioids are a class of pain relieving medications that include the illicit drug heroin as well as the prescription medications oxycodone, hydrocodone, codeine, morphine and fentanyl. Virtually everyone experiences moderate or severe pain at some point in their lifetime. More than 30% of Americans have some form of chronic pain[5,6], so it is unsurprising that opioids are the third most commonly prescribed class of medications in the United States behind antimicrobials and antidepressant.[7] In 2012 alone, 259 million opioid prescriptions were written in the US, which is more than enough to give every American adult their own bottle of pills.[2] The same year, 6.9% of adults aged 20 and over (approximately 19 million Americans) reported using a prescription opioid analgesic in the past 30 days.[8] In 2016, a staggering 12% of Americans had a prescription for opioids.[9-11] Fortunately, progress has been made in reducing opioid prescriptions.

Since the height of opioid prescribing in 2012, there has been a 12% decrease in opioid prescriptions in the last three years.[12] This decrease equates to nearly 17 million fewer filled prescriptions in 2015 alone.[12] Declines were seen in every state in the country except for South Dakota .[12] The US Drug

Enforcement Administration (DEA) finalized an order to reduce production quotas for a variety of Schedule II medications which include opioids by 25%.[13] Despite this decrease, opioid overdose deaths continue to reach new highs.[1] The increase in overdose death, despite nationwide decreases in opioid prescriptions could signal a paradigm shift to people using illicit drugs like heroin. A constellation of factors came together in the previous few decades to trigger the cascade of opioid prescriptions and subsequent overdoses.

Although opioids have been present in America for centuries, it wasn't until the 1990s that opioid use began to accelerate rapidly due to several factors. Low-quality, but influential studies published in the 1980s reported a minimal risk of addiction in patients using opioids.[14,15] Another article published in 1990 reiterated the widespread belief that "therapeutic use of opiate analgesics rarely results in addiction".[16] Relief of pain is one of the fundamental obligations of medical professionals; decreasing patient's pain while not increasing their addiction risk was highly influential on prescribing patterns. These studies and the growing pharmaceutical industry led to the trend in the liberalization of the use of opioids for the treatment of pain.

Pharmaceutical influence peaked in 1996 with the release of OxyContin by Purdue Pharmaceuticals, a more addiction-prone formulation of oxycodone. By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States.[17] In 2015 approximately 1,000 overdose deaths were attributed to OxyContin.[18] Soon after the introduction of OxyContin, the Joint Commission embraced the concept of "Pain as the 5th Vital Sign" and penned a report sponsored by Purdue Pharmaceuticals (the makers of OxyContin) stating that some clinicians have inaccurate and exaggerated concerns about the addiction risk of opioids.[19]

Welfare and health care reform in the 1990's also played a role in the overreliance on opioids.[20] Managed care organizations recognized that opioids were less expensive than comprehensive pain

management clinics and therefore stopped reimbursement for those services.[5] Payers were unwilling to cover non-pharmacological interventions, leaving opioids as one of the few therapeutic options. The embrace of opioids by the scientific community in part due to these highly influential factors lead to changes in physician prescribing practices causing a surge in opioid prescriptions.[21]

This rise in prescriptions correlated with a rapid increase in opioid-related morbidity and mortality due to their intrinsic addictive properties.[22] Medical providers need to ensure that patients' pain is properly assessed and managed; however, that obligation needs to be balanced with the responsibility of not limiting the exposure to risk of addiction. It was difficult to predict the far-reaching downstream effects of these medications that would eventually lead to an epidemic of overdose.

Opioid medications exert their analgesic effect by primarily binding to mu-opioid receptors in the brain. When opioids attach to these receptors, they reduce the perception of pain and produce a sense of euphoria, leading to positive reinforcement. An innate and hazardous property of opioids is their tendency, especially when used repeatedly over time, to induce tolerance. Tolerance occurs when the person no longer responds to the drug as strongly as they did at first, thus necessitating a higher dose to achieve the same effect. This tolerance contributes to the risk of addiction and overdose. Some opioids show tolerance after a single dose.[23] In addition, drug dependence or susceptibility to withdrawal symptoms is another clinically important consequence of repeated exposure to escalating dosages of opioids. The question of why some people develop addiction to these inherently addictive medications while others do not is not clear.

Addiction is the end-result of neurochemical changes to the brain that create compulsive drug seeking and drug use behavior. Because of opioids effect on the part of the brain that regulates breathing, excessive use of opioids can cause respiratory depression leading to overdose death. Addiction and overdose can occur in individuals with valid prescriptions for opioids to relieve pain and in nonmedical

users (i.e., using medications that were not prescribed for them or were taken only for the experience or feeling that they caused). Almost 75% of all opioid misuse starts with people taking medication that was not prescribed for them.[24] A study involving 136,000 opioid overdose patients treated in the emergency department in 2010, found that only 13% of those patients had a chronic pain diagnosis.[25] Predictors of overdose have been identified in the literature that can allow health care providers to targeted interventions for those at risk.[26-28]

Risk Factors

Several risk factors contribute to overdose including prior overdose events, obtaining overlapping prescriptions from multiple providers and pharmacies, taking high daily dosages of prescription opioids, having mental illness or a history of alcohol or other substance abuse, and living in rural areas and having low income.[29] A prior overdose is the biggest risk factor for a future overdose.[30] Higher dosages were associated with an increased risk of overdose compared to lower dosages (1 to < 20 MME/day).[31] Extended-release (ER) and Long-acting (LA) opioids were also associated with an increased overdose risk compared with short-acting opioids. Having overlapping prescriptions was also strongly associated with increased risk of overdose.[32-33] Overdose risk also increases with the concomitant use of certain other medications including muscle relaxants and benzodiazepines.[34]

Muscle relaxants, in addition to opioids and benzodiazepines compose the “triple threat” of overdose. When combined, these medications are synergistic in their potential to cause respiratory depression increasing the risk of death. It is well known that opioid overdoses often involve more than one of these medications. Opioid users often use muscle relaxants and benzodiazepines to augment the effect of euphoria. In opioid users, combining the effects of benzodiazepines enhances the positive subjective effects of opioids.[35]

Turner and Liang found that overdose risk increased with increasing duration of benzodiazepine treatment.[36-37] Use of ≥ 4 pharmacies or prescribers in the past year was both associated with an increased overdose risk.[38] Opioid-related deaths are higher in rural areas even after adjusting for population density.[39] White patients have almost twice the overdose rate as black patients.[40] Inequity in pain management with more restrictive use of opioids for black patients compared to white patients can partly explain these racial differences.[41-43] Substance use disorder diagnoses including opioid use disorder (OUD) were associated with an increased risk of overdose.

OUD is the problematic pattern of opioid use leading to clinically significant impairment or stress.[44] Symptoms of OUD include a strong desire for opioids, inability to control or reduce use, and development of tolerance. This primary, chronic, and relapsing brain disorder currently affects 2.5 million Americans and continues to affect more every year.[45,4] Even with treatment, the underlying vulnerability to addiction never disappears. The chronicity and relapsing nature of OUD are like other chronic conditions that are difficult to treat (e.g., hypertension and diabetes). OUD has penetrated every societal demographic including race, socioeconomic status, and gender.

Men have higher rates of OUD, as do patients between ages 35 to 54 years, whites, and American Indians/Alaska natives.[46] OUD is a clear predictor of overdose; therefore, it is important to look at all potential overdose factors for evaluating one's overdose risk including socioeconomic status. For example, Medicaid enrollees are diagnosed with OUD at a rate of 8.7 per 1,000, over 10 times higher than populations who receive coverage under private insurance companies.[47,48]

The opioid epidemic has a disproportionate impact on Medicaid enrollees. Medicaid enrollees are prescribed opioids at twice the rate of non-Medicaid enrollees.[49,50] These prescribing practices among Medicaid enrollees have led to a three times higher risk of overdose compared to non-Medicaid

patients.[49] Given the asymmetric impact of the opioid epidemic on Medicaid enrollees, it is especially important to study this vulnerable population to develop strategies to prevent overdose.

In response to this disparity, Medicaid has implemented several national and statewide policies. Centers for Medicare and Medicaid Services (CMS) "best practice" policies for addressing prescription opioid overdose and misuse include pharmacy benefit management strategies such as reassessing preferred drug list (PDL) placement, introducing clinical criteria, prior authorization, step therapy, quantity limits, and implementing drug utilization review (DUR) processes.[50,51] Some states have adopted new limits to the number of opioid pills that physicians can prescribe. 46 states have adopted quantity limits and 45 states had adopted prior authorization targeted at opioid harm reduction.[52] Medicaid is the single largest source of insurance for behavioral health services and OUD treatment, so improving and expanding treatment in this population is crucial.[53]

Heroin is a highly addictive drug that is derived from the opium plant. Heroin was a popular pain treatment in the late 1880, but was quickly found to be addictive. Heroin was classified as a Schedule 1 drug under the Controlled Substances Act of 1970, making it illegal to prescribe.[54] Despite these barriers, heroin use continued to increase in the United States. The most common demographic of a heroin user switched from a young urban African-American male in the 1970s to a middle-aged white female from rural America.[17] In the US, heroin use is the highest it has been in the last twenty years.[55,56] Numerous studies indicate that prescription opioids have a gateway effect on subsequent heroin users, with 4 out 5 heroin users stating that their opioid use began with prescription opioids.[57-59]

Prescription opioid users have recently started shifting to heroin, which has a cheaper street value, higher purity, and is easier to obtain.[60] Due in part to these factors, deaths due to heroin has been increasing precipitously in the last several years. In addition to the risk of overdose, IV drug use involving heroin has been implicated in many other medical conditions including human immunodeficiency virus

(HIV) and hepatitis C virus (HCV) infection. The relationship between heroin and prescription opioids emphasizes the importance that neither issue should be addressed in isolation.

Fentanyl has played an increasing role in overdoses since 2013. Fentanyl is a synthetic opioid that is 50-100X more powerful than morphine and 30-50X more powerful than heroin, making it an extremely potent opioid.[61] Fentanyl can rapidly suppress respiration causing death more quickly than do other opioids. From 2012 through 2014, the number of reported deaths involving fentanyl more than doubled; from 2628 to 5544.[62] The relatively low production cost of fentanyl and increasingly high death toll poses a challenging problem in efforts to combat the opioid epidemic. Fentanyl is often mixed with heroin as a combination product often without the user's knowledge. Besides the role of opioids in overdose, there are also non-opioid medications taken in combination with opioids that has implications in overdoses.

Benzodiazepines and opioids taken together increase the risk the overdose by a factor of 4.[31] Benzodiazepines are involved in 30% of drug overdoses involving opioids.[63] Although the benzodiazepines effect of respiratory depression in the brain is mild, the concurrent use with opioids has the potential to increase and/or prolong the respiratory-depressant effect of opioids.[64] The number of individuals prescribed both an opioid and a benzodiazepine increased by 41% between 2002 and 2014.[65] Approximately 50% of those co-prescriptions came from the same physician on the same day.[66] From 2004 to 2011, the rate of ED visits involving the non-medical use of both drug classes increases significantly and overdose deaths nearly tripled.[65] The Food and Drug Administration (FDA) just released its strongest "box" warning on product labels that details the dangers of concomitant use of opioids and benzodiazepines. Evaluation of use of other potentially dangerous non-opioid medications like benzodiazepines is important part of addiction treatment. Although rates of spontaneous recovery from addiction and OUD are low, outcomes can be improved with medication-assisted treatment (MAT).

Mediation-Assisted Treatment

The primary evidence-based treatment for OUD is MAT which includes FDA-approved medications methadone, buprenorphine and naltrexone. Behavioral counseling is also a crucial component of MAT. MAT significantly increases adherence to treatment and reduces illicit opioid use compared with non-drug approaches. Patient with OUD receiving MAT as part of their addiction treatment are 75% less likely to overdose than those note receiving MAT.[67] Unfortunately, these medications are markedly underutilized with fewer than half of OUD patients receiving MAT.[68] Provider-level and policy-level barriers exist that restrict or severely limits patients from accessing MAT. Full integration of the continuum of services for OUD with the rest of health care is crucial.[69]

Buprenorphine, a partial opioid agonist which can be given in outpatient clinics, was approved for the treatment of opioid addiction in 2002 by the Drug Addiction Treatment Act of 2000.[70] Buprenorphine is becoming the gold standard for OUD treatment. As a treatment for OUD, buprenorphine decreases withdrawal, craving, and opioid use.[26] Medical providers must obtain a waiver to prescribe buprenorphine, because prior to DATA 2000 such treatment was not permitted outside the traditional opioid treatment program (OTP) setting. Twelve years after buprenorphine approval, as of 2014 only 2.2% of US physicians obtained the necessary waiver to prescribe buprenorphine. Most US counties (53.4%) do not have a single prescriber of medications to treat OUD.[68] This equates to 30 million Americans living in counties that do not have a buprenorphine-waivered physician.[71]

Fortunately, there has been a steady increase in the number of physicians obtaining the waiver. However, 40% of physicians with a waiver do no prescribe buprenorphine at all.[45] Novice prescribers cite insufficient access to more-experienced prescribers and insufficient access to substance abuse counseling, a necessary component of buprenorphine treatment.[72] The Comprehensive Addiction and Recovery Act (CARA) signed into law in July 2016, will extend buprenorphine privileges to nurse

practitioners (NPs) and physician assistants (PAs) starting in early 2017.[73] Extending buprenorphine prescribing privileges to mid-level providers should help increase buprenorphine access to patients with OUD.

Buprenorphine waivered physicians were limited to treating 30 patients with OUD in the first year, and then 100 in subsequent years. This restriction was a limiting factor, preventing some patients from receiving MAT. Restricting prescribers to treating a maximum of number of patients is unique to buprenorphine. Only a slight majority of waivered providers actually prescribe buprenorphine and most these providers do not prescribe to their maximum patient limit.[74,75] This equates to the reality that only minority of waivered providers are providing most of the buprenorphine prescriptions.

A recent survey found that 66% of addiction specialists reported that their patient demand for treatment exceeded the 100-patient prescribing limit.[76] The irony of restricting buprenorphine, but not opioids, the very medication that has led to the need for buprenorphine is being remedied. Under new SAMHSA regulations, prescribers who have prescribed buprenorphine to 100 patients for at least one year can apply to increase their limit to 275 in July 2016. This is certainly a much-needed increase from the initial limit of 10 patients in 2002, however the number of number of people with OUD has also increased 125% from 2002.[77]

Methadone is a potent synthetic opioid agonist that binds to the μ-opioid receptor, thereby reducing neuropathic pain. Methadone also blocks the opioid euphoric effect, thereby reducing the cravings and withdrawal symptoms caused by opioid use. Methadone has been used since 1972 to treat opioid addiction and is the most widely available pharmacotherapy for opioid addiction. Methadone significantly lowers illicit opioid use and opioid overdose.[78] Although, methadone is an effective treatment of OUD, its use for the treatment of pain has been linked to thousands of overdose deaths each year.[1] There was no difference found in OUD treatment outcomes between methadone and

buprenorphine.[79] Significant access barriers to methadone include long waiting lists for treatment entry, limited geographic coverage, limited insurance coverage, and the requirement of daily visits at Opioid Treatment Programs.

Naltrexone is semi-synthetic mu and kappa opioid receptor antagonist that blocks opioid addictive effects. Unlike methadone and buprenorphine, naltrexone is without intrinsic activity and poses minimal risk of abuse or diversion.[80] There are no randomized double-blind controlled trials comparing all three medications. Individually, these medications have superior OUD treatment outcomes compared to non-medication based therapies. Even when someone with OUD desires treatment, there are obstacles of starting treatment including the presence of psychological comorbidities and barriers to access.

Access to Care

MAT is widely available, however, there are systematic barriers including inadequate funding for treatment programs and lack of insurance coverage prevent people living with addiction from accessing these vital medications. Among public insurance plans, only 28 states currently cover all three FDA-approved MAT medications.[81] Although the ACA requires many insurers to cover addiction treatment benefits under the essential health benefit (EHB), it does not specify which benefits must be covered.[82] Many policies impose treatment-limiting prior authorization requirements, place arbitrary limits on medication dosage and length of treatment. Numerous private health insurance plans exclude coverage of methadone maintenance treatment, even though it is proven to be the effective treatment option for many people with OUD.[83]

Access to MAT is challenging especially in rural areas. An important aspect of the opioid epidemic is the lack of treatment options for the millions of Americans living in rural communities. Overdose death rates are 45% higher in nonmetropolitan areas.[2,84] One avenue to reduce the coverage gap in rural medicine is connecting physicians with patients remotely through telemedicine. Telemedicine can increase access to

addiction treatment service by removing the barriers of geography and stigma.[85] The hub-and-spoke model is another initiative that connects community health centers and private practitioners with central, specialized substance abuse treatment programs after stabilizing the patient using MAT.

The emergency department is becoming a battleground for patients with opioid addiction. In 2011, approximately 420,040 ED visits were related to use of opioids.[86] For every opioid overdose, there are 10 treatment admissions and 32 ED visits.[87] Patients with OUD are increasingly seeking medical care in emergency departments not only for OUD-specific treatment, but also trauma, illness, and chronic medical conditions. Even though patients with OUD are seeking treatment in the ED, their treatment needs are not being met. Thousands of patients with OUD receive medical treatment to relieve opioid withdrawal only during brief detoxification admissions. Afterwards, these patients lose their tolerance to opioids, and are discharged with referrals to medication-free residential or outpatient care.[88] Of those patients, 70-90% quickly relapse and face a high risk of overdose death.[89]

Emergency departments have an opportunity to initiation treatment for patient with OUD who may not otherwise utilize healthcare. Emergency department initiated MAT referral to patients with OUD has already been shown to reduce illicit opioid use.[90] Patients with OUD are more likely to receive MAT, and therefore reduce opioid use long-term if they are started on MAT in the emergency department.[91] In addition, patients who initiated buprenorphine in the emergency department were more likely to remain in formal addiction treatment after 2 months compared to groups that were either referred for MAT.[91]

For every fatal overdose, up to 30 nonfatal overdoses occur.[92] Most long-term heroin users experience at least one nonfatal dose in their lifetime.[93] People experienced non-fatal overdoses face high rates of chronic morbidity following injuries sustained during the overdose event such as renal failure and anoxic brain injury.[94] Furthermore, non-fatal overdoses are a predictor for future fatal overdoses.[20] Non-fatal

overdoses are likely underreported due to the increasing public availability of Naloxone, a medication which can reverse the effects of an opioid overdose.

The preventable nature of these overdoses represents opportunities for health care providers to intervene to mitigate risks of future overdoses. Most fatal overdoses occur when the patient is not enrolled in a long-term, stable drug treatment.[95] Potential responses include reassessing opioid prescribing and referring patients to addiction treatment. A study of commercially-insured patients indicated that high rates of prescription opioid use occurred after a nonfatal overdose suggesting that health systems could play a major role in informing opioid prescribers about patient's addiction risk.[96] Understanding addiction risk could also lead to increased awareness and use of Naloxone.

Naloxone is a rapid-acting μ opioid-receptor antagonist that reverses the effects of an opioid overdose by displacing the harmful opioid from the receptor. Naloxone has reversed thousands overdoses since its FDA approval in 1971 as an antidote for opioid overdose.[97] Studies have shown that Naloxone could cut the overdose death rate by 50%.[98] Many states have allowed people to obtain Naloxone without a prescription, removing an important barrier to receiving the life-saving medication. In addition, first responders including EMTs, police, and firefighters are now authorized to use Naloxone. However, other barriers remain including the cost of the medication and education of the proper use of the medication.

Patients taking opioids for chronic pain who received information education and a prescription for Naloxone had 63% fewer opioid-related emergency department visits in one year than patients not receiving education and Naloxone.[20] Naloxone is a safe, highly effective rescue medication and has no potential for abuse or dependency. Removing barriers for the use of Naloxone for opioid overdose is vital. Although MAT is effective is reducing opioid addiction, many patients do not complete addiction treatment regimens due to the chronic and relapsing nature of addiction.[99]

Pennsylvania Epidemiology

The opioid epidemic has had a disproportionate effect on Pennsylvanians, with 3,505 overdose deaths in 2015, a 30% increase from the previous year.[100] This represents a 14-fold increase in the last 35 years.[101] Pennsylvania has the sixth highest overdose death rate in the country at 26.3 overdose deaths per 100,000 compared to 16.3 deaths per 100,000 in the US.[102] The death rate involving heroin is 5.6 per 100,000 residents, 37% higher than the national average.[2] Pennsylvania leads the nation in the number of drug overdoses in men ages 12-25.[103] There have been several state-specific initiatives to reduce overdoses in Pennsylvania including changing emergency department guidelines.

Limiting ED opioid prescriptions to seven days is a new guideline that is being discussed in several states across the country, including Pennsylvania.[104] In addition, these guidelines also state that ED physicians may not write prescriptions for refills of opioids and ED physicians are required to refer individuals for treatment if the individual is believed to be at risk for substance abuse. These guidelines took effect on January 1st, 2017. These guidelines emphasize the importance of health care providers taking a more active role in the prevention and treatment of opioid addiction. Pennsylvania recently updated their prescription drug monitoring program (PDMP) to prevent prescription drug abuse in the state.

Effective January 1, 2017 prescribers must query the PDMP each time a patient is prescribed an opioid or benzodiazepine by the prescriber. In addition, dispensing prescribers or pharmacies must now submit data to the PDMP no later than the close of the subsequent business day after dispensing the controlled substance. Across the country, implementation of PDMP has shown reduction in opioids dispensed and opioid-related mortality.[105-110]

Study

Objective

While MAT rates have increased over time, less is known about MAT use before or after overdoses, even in OUD patients. Thus, we compared prescription opioid and MAT use in patients before and after heroin or prescription opioid overdoses in a sample of Medicaid enrollees.

Methods

We collected 2008-2013 Medicaid enrollee claims data from the Pennsylvania Department of Human Services for all managed care (75%) and fee-for-service (25%) enrollees. Our sample included enrollees aged 12-64 years old with ≥6 months of continuous Medicaid enrollment before an overdose (with prescription opioids or heroin) that resulted in a Medicaid claim. We excluded enrollees who left Medicaid or died within 6 months of the overdose from the post-overdose measures to ensure complete follow-up but included them in the pre-overdose measures for completeness. We used a logistic regression model with correlated data analysis to examine the differences in MAT and rates of prescription opioid use (any and cumulative days' duration) pre-overdose and post-overdose and stratified analyses by the type of non-fatal overdose (opioid vs. heroin). All analyses were performed in SAS version 9.4 (SAS Institute, NC). This study was deemed exempt by the University of Pittsburgh Institutional Review Board.

Results

Among 3,009 enrollees who had a heroin overdose and 4,989 who had a prescription opioid overdose, most were <40 years old and white (**Table 1**). Among those with heroin overdose, 68.7% survived and were still enrolled in Medicaid 6 months post-overdose compared to 79.1% in the opioid group. Among

those who survived after the non-fatal overdose, opioid use did not change in the heroin group (40.6% pre and 39.7% post, P = 0.12, **Figure 1**) whereas enrollees in the opioid group were less likely to fill opioid prescriptions post-overdose (65.4% to 59.6% p < 0.001). Likewise, the percent of enrollees with ≥90 days duration of opioids did not change in the heroin group pre- to post-overdose (9.4% to 9.0%, P =0.07) but decreased in the opioid group (32.2% to 28.3%, P < 0.001). MAT increased after overdose in the heroin (28.7% to 33.0%, P < 0.001) and opioid group (from 13.6% to 15.1%, P = 0.001). Sensitivity analyses limiting the samples to only those diagnosed with OUD yielded similar findings. Among patients with OUD pre-overdose there was a significant decrease in greater than 180 opioid days supply post-overdose compared to pre-overdose in the opioid group (17.7% pre and 13.0% post, p<0.001, **Table 2**). In contrast, there was no significant difference among greater than 180 opioid days' supply post-overdose in enrollees with OUD in the heroin group (3.6% pre and 3.8% post, P=0.91, **Table 3**). In enrollees with and without an OUD diagnosis there was significant decrease in greater than 180 opioid days' supply post-overdose compared to pre-overdose in the opioid group (19.8% pre and 15.8% post, p<0.001, **Table 4**). In the heroin group, there was significant difference in greater than 180 opioid days supplied post-overdose compared to pre-overdose (4.3% pre and 4.0% post, P=0.96, **Table 5**). Among enrollees with an OUD diagnosis there was a decrease pre-overdose and post-overdose in both the opioid (52.5% pre and 44.9% post, p<0.001) and heroin (83.3% pre and 61.4% post, P<0.001) groups. There was no difference in benzodiazepine use post-overdose compared to pre-overdose in either the opioid group (46.9% pre and 45.2% post, P=0.10) and heroin group (38.3% pre and 36.6% post, P=0.20). There was no difference in muscle relaxant use post-overdose compared to pre-overdose in either the opioid group (26.2% pre and 24.7% post, P=0.11) and heroin group (15.0% pre and 15.8% post, P=0.48).

Discussion

MAT after overdoses increased in both the heroin and opioid groups. There was no change in opioid duration and use in the heroin group, whereas both measures declined in the opioid group. These

findings represent a missed opportunity to better engage enrollees with overdose sentinel events. Potential interventions to reduce future overdose events include trigger notifications to prescribers on patient overdose events to increase MAT and decrease potentially unsafe opioid prescribing. Furthermore, ED MAT initiation referral to patients with OUD has already been shown to reduce illicit opioid use.[92] The opioid group showed a decrease in days' supply of opioid, compared to the heroin which did show any change post-overdose. This difference could be related to better prescriber awareness of overdose due to prescription opioids compared to heroin. In addition, this reduction could be due to increased recognition of the dangers of prescribing a large amount of opioids as delineated by several opioid prescribing recommendations that have been released over the last several years. The fact that there was no change in benzodiazepine use or muscle relaxant use after overdose is troubling. Benzodiazepines and muscle relaxants in addition to opioids make of the "triple threat" of overdose risk. Further interventions should be targeted at decreasing benzodiazepine and muscle relaxant use including added warning labels to these medications and health system interventions such as prescription caps and prior authorization. A limitation of this study is that actual use of prescription use is difficult to assess using claims data.

Appendix: Tables and Figures

Table 1: Characteristics of Medicaid Enrollees with Opioid and Heroin Overdose Events

	Heroin overdose		Opioid overdose	
Characteristics	Pre-overdose[1], N = 3,009	Post-overdose[2], N = 2,068	Pre-overdose, N = 4,989	Post-overdose, N = 3,945
	N (%)	N (%)	N (%)	N (%)
Age				
12-17	41 (1.4)	37 (1.8)	277 (5.6)	251 (6.4)
18-29	1514 (50.3)	981 (47.4)	1572 (31.5)	1210 (30.7)
30-39	720 (23.9)	503 (24.3)	1186 (23.8)	950 (24.1)
40-49	464 (15.4)	338 (16.3)	1083 (21.7)	880 (22.3)
50-64	270 (9.0)	209 (10.1)	871 (17.5)	654 (16.6)
Gender				
Female	1410 (46.9)	1001 (48.4)	2938 (58.9)	2431 (61.6)
Race				
White	2467 (82.0)	1677 (81.1)	3777 (75.7)	2958 (75.0)
Black	253 (8.4)	184 (8.9)	827 (16.6)	677 (17.2)
Hispanic	234 (7.8)	164 (7.9)	278 (5.6)	220 (5.6)
Other	55 (1.8)	43 (2.1)	107 (2.1)	90 (2.3)
Type of Eligibility				
SSI	451 (15.0)	374 (18.1)	1228 (24.6)	1042 (26.4)
TANF	635 (21.1)	464 (22.4)	1178 (23.6)	979 (24.8)
General Assistance[3]	1088 (36.2)	635 (30.7)	1011 (20.3)	713 (18.1)
Other	835 (27.8)	595 (28.8)	1572 (31.5)	1211 (30.7)
Opioid Day Duration				
0 days (no fills)	1787 (59.4)	1246 (60.3)	1728 (34.6)	1592 (40.4)
< 30 days	710 (23.6)	483 (23.4)	1111 (22.3)	814 (20.6)
≥ 30 & < 90 days	228 (7.6)	152 (7.4)	545 (10.9)	422 (10.7)
≥ 90 & < 180 days	151 (5.0)	104 (5.0)	624 (12.5)	501 (12.7)
≥ 180 days	133 (4.4)	83 (4.0)	981 (19.7)	616 (15.6)
OUD Diagnosis[4]	2505 (83.3)	1490 (72.1)	2614 (52.4)	1674 (42.4)

Notes:

1. Overdose evets were defined by ICD-9 codes 965.00, 965.01, 965.02, 965.09, E.850.0, E850.1, E.850.2. We including only the first overdose event for those with multiple overdoses.
2. Post-overdose measures of opioid day duration and OUD diagnosis do not include those lost to follow-up due to disenrollment (n = 792, 15.9%) or death (n = 252, 5.1%) from Medicaid in the opioid overdose group or disenrollment (n = 808, 26.9%) or death (n = 133, 4.4%) from the heroin overdose group.
3. General Assistance (GA) is state-funded assistance that provides money and other services for eligible individuals who do not meet the requirements of federally funded programs such as Temporary Assistance for Needy Families (TANF).
4. Pre-overdose OUD diagnosis was recorded on an inpatient, outpatient or professional claim in the 6 months before and including the overdose event. Post-overdose diagnoses were recorded >=1 day after the overdose event up to 6 months post-overdose to avoid including the overdose event in the definition of OUD.

Table 2: Medication use and medication-assisted treatment use pre vs. post-opioid overdose among those with OUD in pre-overdose period			
Outcomes	**Pre-overdose (n=2621)**	**Post-overdose[1] (n=2015)**	
Medication Use	**N (%)**	**N (%)**	**p-value**
Any opioid use	1663 (63.5)	1166 (57.9)	<0.001
Opioid Day Supply			
0 days (no fill)	963 (36.7)	855 (42.4)	
<30 days	595 (22.7)	429 (21.3)	
>= 30 & <90 days	295 (11.3)	231 (11.5)	<0.001
>=90 & < 180 days	305 (11.6)	238 (11.8)	
>= 180 days	463 (17.7)	262 (13.0)	
MAT use			
Methadone	413 (15.8)	321 (15.9)	0.87
Buprenorphine	247 (9.4)	213 (10.6)	0.20
Naltrexone	24 (0.9)	23 (1.1)	0.45
Any MAT	653 (24.9)	528 (26.2)	0.32

Table 3: Medication use and medication-assisted treatment use pre vs. post-heroin overdose among those with OUD in pre-overdose period			
Outcomes	**Pre-overdose (n=2242)**	**Post-overdose[1] (n=1529)**	
Medication Use	**N (%)**	**N (%)**	**p-value**
Any opioid use	910 (40.6)	617 (40.4)	0.88
Opioid Day Supply			
0 days (no fill)	1339 (59.7)	916 (59.9)	
<30 days	549 (24.5)	368 (24.1)	
>= 30 & <90 days	166 (7.4)	121 (7.9)	0.91
>=90 & < 180 days	108 (4.8)	66 (4.3)	
>= 180 days	80 (3.6)	58 (3.8)	
MAT use			
Methadone	257 (11.5)	214 (14.0)	0.02
Buprenorphine	476 (21.1)	336 (22.0)	0.59
Naltrexone	64 (2.9)	51 (3.3)	0.40
Any MAT	730 (32.6)	549 (35.9)	0.03

Table 4: Medication use and medication-assisted treatment use pre vs. post-opioid overdose			
Outcomes	**Pre-overdose, N = 4,997**	**Post-overdose[1] N = 3,952**	
Medication Use	**N (%)**	**N (%)**	**p-value**
Opioid use	3279 (65.6)	2372 (60.0)	<0.001
Benzodiazepine use	2345 (46.9)	1786 (45.2)	0.10
Muscle Relaxant use	1311 (26.2)	978 (24.7)	0.11
Opioid + benzodiazepine + muscle relaxant use	815 (16.3)	576 (14.6)	0.02
Opioid Prescription Days Supply			
0 days (no fills)	1729 (34.6)	1592 (40.3)	
<30 days	1112 (22.2)	817 (20.7)	
>= 30 & <90 days	547 (11.0)	424 (10.7)	<0.001
>=90 & < 180 days	619 (12.4)	495 (12.5)	
>= 180 days	990 (19.8)	624 (15.8)	
OUD Diagnosis[2]	2621 (52.5)	1774 (44.9)	<0.001
MAT use			
Methadone	413 (8.3)	329 (8.3)	0.92
Buprenorphine	269 (5.4)	265 (6.7)	0.009
Naltrexone	29 (0.6)	31 (0.8)	0.24
Any MAT[3]	680 (13.6)	595 (15.1)	0.05

Table 5: Medication use and medication-assisted treatment use pre vs. post-heroin overdose			
Outcomes	**Pre-overdose N = 2,693**	**Post-overdose[1] N = 1,848**	
Medication Use	**N (%)**	**N (%)**	**p-value**
Opioid use	1109 (41.2)	742 (40.2)	0.48
Benzodiazepine use	1032 (38.3)	674 (36.5)	0.20
Muscle Relaxant use	405 (15.0)	292 (15.8)	0.48
Opioid + benzodiazepine + muscle relaxant use	166 (6.2)	116 (6.3)	0.88
Opioid Prescription Days Supply			
0 days (no fills)	1591 (59.1)	1110 (60.1)	
<30 days	655 (24.3)	438 (23.7)	
>= 30 & <90 days	197 (7.3)	136 (7.3)	0.96
>=90 & < 180 days	134 (5.0)	90 (4.9)	
>= 180 days	116 (4.3)	74 (4.0)	
OUD Diagnosis[2]	2242 (83.3)	1134 (61.4)	<0.001
MAT use			
Methadone	257 (9.5)	233 (12.6)	0.001
Buprenorphine	508 (18.9)	376 (20.3)	0.22
Naltrexone	68 (2.5)	56 (3.0)	0.30
Any MAT[3]	766 (28.4)	608 (32.9)	0.001

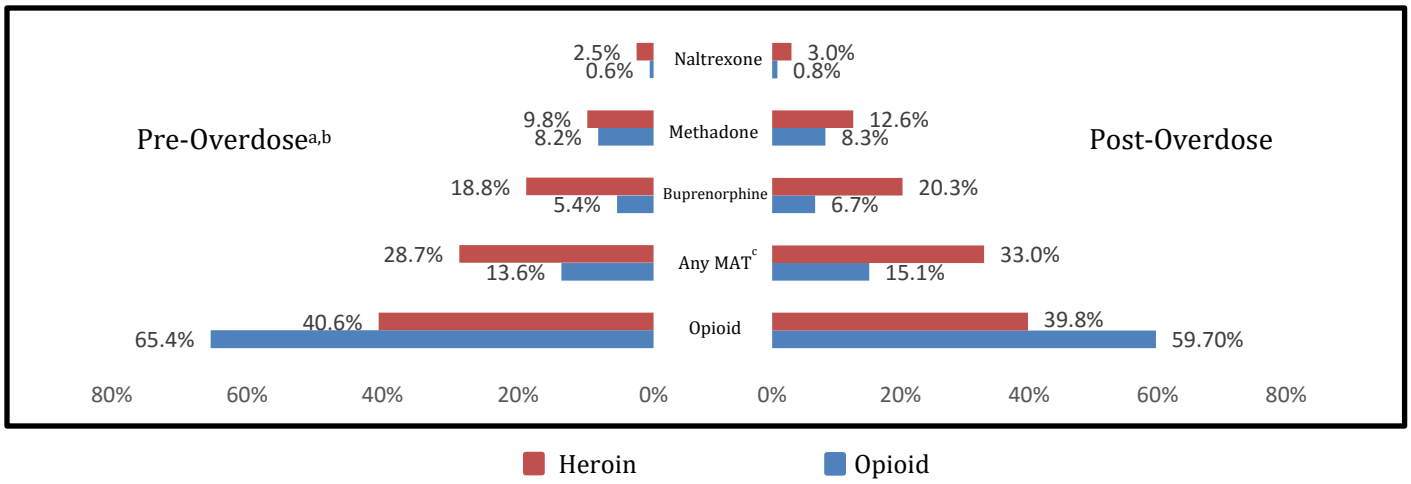

Figure 1: Medication use pre- and post-overdose (2008-2013)

[a] We identified 3,009 enrollees in the heroin group pre-overdose and 2,068 post-overdose. We identified 4,989 enrollees in the opioid group pre-overdose and 3,945 post-overdose.

[b] We identified overdose events by type (due to heroin or opioids) using ICD-9 codes (965.01, 965.00, 965.02, 965.09, E.850.1, E.850.2) in inpatient, outpatient, and professional claims.

[c] Defined as any medication-assisted treatment (MAT). Some enrollees were prescribed > 1 MAT.

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