Opioid Agonist Treatments and Heroin Overdose Deaths in Baltimore, Maryland, 1995–2009

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Objectives. We examined the association between the expansion of methadone and buprenorphine treatment and the prevalence of heroin overdose deaths in Baltimore, Maryland from 1995 to 2009.

Methods. We conducted a longitudinal time series analysis of archival data using linear regression with the Newey–West method to correct SEs for heteroscedasticity and autocorrelation, adjusting for average heroin purity.

Results. Overdose deaths attributed to heroin ranged from a high of 312 in 1999 to a low of 106 in 2008. While mean heroin purity rose sharply (1995–1999), the increasing number of patients treated with methadone was not associated with a change in the number of overdose deaths, but starting in 2000 expansion of opioid agonist treatment was associated with a decline in overdose deaths. Adjusting for heroin purity and the number of methadone patients, there was a statistically significant inverse relationship between heroin overdose deaths and patients treated with buprenorphine ($P = .002$).

Conclusions. Increased access to opioid agonist treatment was associated with a reduction in heroin overdose deaths. Implementing policies that support evidence-based medication treatment of opiate dependence may decrease heroin overdose deaths. (*Am J Public Health.* 2013;103:917–922. doi:10.2105/AJPH.2012.301049)

Heroin overdose death is a major public health problem throughout the world.[1–4] Factors thought to be related to the prevalence of heroin overdose death include the availability and purity of heroin on the streets,[5–8] periods of brief incarceration or detoxification that lower opioid tolerance,[9–14] and the availability and penetration of opioid agonist treatment.[1,15–17] Among public health treatment strategies to reduce opioid overdose deaths are increasing opioid agonist maintenance treatments, such as those involving methadone and buprenorphine; using depot naltrexone[18]; and distributing naloxone.[19,20]

In Baltimore, Maryland, throughout the 1990s, heroin use and addiction were associated with an alarming number of overdose deaths, and from 1990 to 1997 drug overdose deaths increased by 426%, an increase that exceeded that of all the other 26 major US cities reporting to the federal Drug Abuse Warning Network during the same period.[21] Starting in 1998, city and state leaders and local foundations renewed efforts to expand access to drug abuse treatment to reduce the impact of heroin and other drug addiction. The city obtained increased state and city funding for drug abuse treatment and reformed zoning laws to ease the opening of new drug abuse treatment programs. Through these efforts, the city's methadone treatment capacity increased significantly over the next 6 years.

With the passage of the Drug Abuse Treatment Act of 2000 and the Food and Drug Administration's approval of buprenorphine for the treatment of opioid dependence,[22] buprenorphine became available through private physician offices and in some community health centers in Baltimore. Maryland added buprenorphine to its Medicaid formulary in 2003 and organized efforts to enroll patients in Medicaid. In late 2006, the Baltimore City Health Department and the local substance abuse authority, the Baltimore Substance Abuse Systems, Inc., funded an initiative to expand access to buprenorphine treatment through formerly drug-free outpatient clinics and physicians' offices by providing funding for Baltimore City physicians to obtain training and the necessary federal license to prescribe buprenorphine. This initiative integrated buprenorphine into the Baltimore Substance Abuse Systems, Inc.–funded network of drug-free outpatient clinics and created a system, overseen by the local nonprofit Baltimore Healthcare Access, to transfer stabilized buprenorphine patients to primary care physicians in community health centers and other primary care sites for ongoing care. From 2006 through 2009, the number of patients treated with buprenorphine in Baltimore City increased substantially.

Through the efforts to expand methadone treatment in regulated opioid treatment programs and the increase in availability of buprenorphine treatment outside such programs, the number of patients treated with these evidence-based medications nearly quadrupled from 1995 through 2009. Meanwhile, heroin overdose deaths declined from a peak of 312 in 1999 to 118 in 2009. We examined the association between the increase in the number of patients treated with methadone and buprenorphine and the decline in heroin overdose deaths. We used archival data obtained from various public and private sources to examine the association between heroin overdose deaths and the increase in methadone and buprenorphine patients, controlling for the average purity of seized heroin in Baltimore City from 1995 through 2009.

METHODS

We obtained the number of 1995–2009 heroin overdose deaths from reports the Baltimore City Health Department generated.[23–26] The methodology used by the Health Department for determining the cause of death is described elsewhere in detail.[23] Briefly, the health department obtained and analyzed intoxication death records from the Maryland

Office of the Chief Medical Examiner. The Baltimore City Health Department classified these deaths as associated with a particular drug if either the drug was mentioned in the Office of the Chief Medical Examiner–determined cause of death or the Office of the Chief Medical Examiner–determined cause of death was reported nonspecifically as "drug intoxication" or "narcotic intoxication" and the toxicological analysis indicated the presence of the drug. In keeping with accepted practices in pathology,[27] the Baltimore City Health Department considered a death to be a heroin overdose death if heroin or its metabolic products, 6-monacetylmorphine, or morphine were found in the body.

Heroin Purity

We obtained data on the estimated annual purity of heroin in Baltimore from 1995 through 2009 from the US Drug Enforcement Agency's (DEA's) Heroin Domestic Monitor Program (DEA, personal written communication, November 2011). The DEA Special Testing and Research Laboratory assesses the purity of retail-level heroin that undercover DEA agents purchase on the streets of 28 cities throughout the United States.[28] In the analysis, we used the average purity of South American heroin that was seized in Baltimore because it had the most samples and was available for all years. In any year, there were far fewer samples of Southeast Asian and Southwest Asian heroin. The DEA analyzed an average of 26 distinct purchases in Baltimore each year over the period we studied and provided us with the mean purity values for every year 1995 through 2009 and the range in heroin purity only for some of these years.

Patients Treated With Methadone or Buprenorphine

We obtained the number of unique patients in methadone treatment for opioid dependence in Baltimore City between 1995 and 2009 for each year from the Maryland Department of Health's Alcohol and Drug Abuse Administration (personal written communication, November 2011). During this period, licensed methadone treatment providers in the city were required to submit basic admission and discharge data through the Alcohol and Drug Abuse Administration's computerized data systems.

We obtained the estimated annual number of unique patients in Baltimore City receiving buprenorphine/naloxone (Suboxone) or buprenorphine (Subutex) from the firm Wolters Kluwer Pharma Solutions (WKPS), which monitors buprenorphine prescriptions in the United States for Reckitt Benckiser, the manufacturer and distributor of buprenorphine. WKPS identified unique patients receiving either buprenorphine formulation from a sample of prescription claims containing encrypted patient identifiers, the name of the medication dispensed, the number of tablets, and the number of days' supply. WKPS used an algorithm to determine the number of prescriptions each patient in the Baltimore sample obtained. WKPS obtained the total prescription volume for buprenorphine in Baltimore from the Source Lx Database. WKPS projected the number of unique patients in Baltimore that were treated with buprenorphine each year from 2003 through 2009, inclusive. WKPS did not track the duration of buprenorphine treatment.

Data Analysis

The collected data represented aggregated city-level information for 15 consecutive years. Thus, we conducted time series analysis of heroin overdose deaths using linear regression with the Newey–West method to correct SEs for heteroscedasticity and autocorrelation.[29] We estimated a series of models to examine the relationship between heroin overdose deaths and the number of patients treated with methadone and those treated with buprenorphine, controlling for average heroin purity. For these analyses, we transformed both the explanatory and outcome variables using first differencing to correct for nonstationarity in the time series.[30] In addition, we natural log–transformed the number of overdose deaths before differencing to stabilize its variance.[31] Thus, this transformed variable represents the percentage change in overdose deaths from year to year. We confirmed our findings using an autoregressive integrated moving average modeling approach. Although the autoregressive integrated moving average yielded somewhat larger SEs than did the Newey–West adjustment, the substantive conclusions were consistent across these 2 techniques.

RESULTS

Table 1 shows the annual number of heroin overdose deaths, the number of patients treated with methadone and buprenorphine, and heroin purity from 1995 through 2009 in Baltimore City.

TABLE 1—Heroin Overdose Deaths, Heroin Purity, and Number of Patients Treated With Buprenorphine and Methadone: Baltimore, MD, 1995–2009

Year	Heroin Overdose Deaths, No.	Heroin Purity, %	Patients Treated With Buprenorphine, No.	Patients Treated With Methadone, No.
1995	245	16.5	. . .	4204
1996	214	23.7	. . .	5473
1997	251	20.0	. . .	4999
1998	270	31.4	. . .	5804
1999	312	37.9	. . .	7317
2000	285	25.0	. . .	7255
2001	245	29.1	. . .	7566
2002	276	23.6	. . .	8089
2003	223	35.0	577	8903
2004	179	27.5	1914	9113
2005	161	29.1	2290	10 084
2006	184	31.0	1795	8751
2007	185	18.1	3573	8062
2008	106	18.9	6767	8270
2009	118	14.1	7479	8359

Descriptive Statistics for 1995–2009

Before treatment expansion, 4204 patients received methadone treatment at some point in 1995. Thereafter, the annual number of methadone patients treated increased steadily to a peak of 10 084 in 2005 and remained nearly double the 1995 number through 2009, when the number was 8359.

Buprenorphine was not available in the United States for the treatment of opioid dependence until fall 2002. As shown in Table 1, the estimated number of patients receiving prescriptions for buprenorphine treatment in Baltimore City rose only modestly from 577 in 2003 to 1795 in 2006 and then rose sharply thereafter to 7479 in 2009. The total number of patients receiving opioid agonist treatment (i.e., methadone and buprenorphine combined) at some point in a given year nearly quadrupled from 1995 through 2009, going from 4204 to 15 838.

Overdose deaths attributed to heroin ranged from a high of 312 in 1999 to a low of 106 in 2008. The decline in overdose deaths began in 2000, and there was a sharp drop from 276 in 2002 to 223 in 2003 before there was any significant availability of buprenorphine. However, the sharpest drop in deaths occurred from 2007 to 2008, when annual heroin overdose deaths decreased from 185 to 106 and patients receiving buprenorphine almost doubled from 3573 to 6767.

Mean heroin purity, which is typically related to its general availability, was 16.5% in 1995, peaked at 37.9% in 1999, and declined unevenly by 2009 to 14.1%. However, the range of purity among samples in a given year varied widely. For example, in 2002—when the number of overdose deaths rose to 276 from 245 in 2001—the purity of South American heroin ranged from 7.1% to 82.6% (26 samples). In that same year the mean purity declined to 23.6% from 29.1% in 2001. In 2007, when the number of deaths had declined to 185, the mean purity of South American heroin had declined to 18.1%, but the range was from 4.5% to 92.0% (23 samples).

We computed simple correlations to gauge the general strength of the linear relationship between heroin overdose deaths and patients treated with methadone, patients treated with buprenorphine, and mean heroin purity. The correlation between heroin overdose deaths and patients treated with buprenorphine was high ($r = -0.88$), indicating a strong inverse linear association between these 2 variables. The correlation between overdose deaths and patients treated with methadone was moderately high ($r = -0.48$), with overdose deaths declining as the number of patients treated with methadone increased. There was also a moderately strong simple correlation between overdose deaths and mean heroin purity ($r = 0.46$). All the raw linear correlations were in the expected direction, with overdose deaths negatively correlated with agonist treatment expansion and positively correlated with heroin purity.

Results of Time Series Analysis

Figure 1 plots the annual number of heroin overdose deaths, the number of patients treated with methadone, and the number of patients treated with buprenorphine for 1995 through 2009.

Over the entire 1995–2009 period, heroin overdose deaths were not significantly associated with mean heroin purity ($P = .68$). From 1995 to 2009, the relationship of heroin overdose deaths to methadone treatment expansion was complex. When we adjusted for heroin purity over the entire period from 1995 to 2009, there was no significant association between changes in heroin overdose deaths and methadone treatment utilization ($P = .532$). Between 1995 and 2002, there was no association between heroin overdose deaths and the number of methadone patients ($P = .957$). By contrast, from 2003—the year buprenorphine treatment became available in Baltimore City—through 2009, there was a significant negative association between heroin overdose deaths and the number of methadone patients ($P = .032$). Similarly, the negative relationship between heroin overdose deaths and the number of buprenorphine patients during this period was significant ($P < .001$).

When we adjusted for both mean heroin purity and the number of methadone patients, there was a strong and statistically significant inverse relationship between heroin overdose deaths and the number of buprenorphine patients from 1995 to 2009 ($P = .002$). The number of methadone patients was not significant in this model. Average annual heroin overdose deaths decreased by 37% after buprenorphine became available in 2003 (average number of heroin overdose deaths between 1995 and 2002 of 262 vs 165 between 2003 and 2009).

Although we focused on heroin overdose deaths, it is important to note that there was an increase in methadone-associated deaths from 1995 to 2009, which peaked at 85 in 2007. Although the number of methadone-related deaths seemed to escalate with the expansion

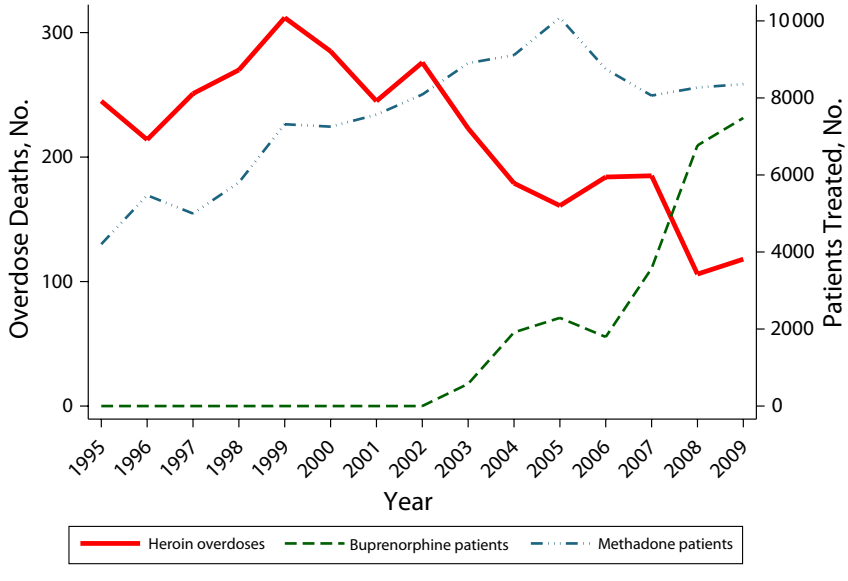

FIGURE 1—Heroin overdose deaths and opioid agonist treatment: Baltimore, MD, 1995–2009.

of methadone treatment, a closer investigation in which we applied the differenced time series model to methadone deaths revealed no significant association between changes in methadone-associated mortality and the expansion of methadone treatment ($P=.718$). Rather, the increases in methadone-associated mortality may reflect a larger national trend in such deaths, which the increased use of methadone for pain management has driven.[32,33]

DISCUSSION

Among US cities, Baltimore had the largest increase in heroin overdose deaths in the 1990s.[21] Starting in 1998, Baltimore City and Maryland State officials launched a concerted effort to decrease heroin addiction and its sequelae in Baltimore. Significant thrusts of this effort were expanding evidence-based treatment of heroin addiction with methadone maintenance—which more than doubled the number of methadone patients treated annually from 1995 through 2009—adding buprenorphine to the Medicaid formulary in 2003, and starting a program of subsidized treatment with buprenorphine in 2006. The association between the increase in the number of buprenorphine patients and the decrease in heroin-related overdose deaths in Baltimore was statistically significant and strong. Buprenorphine is a partial opioid agonist that binds tightly to the μ-opioid receptor, blocking the effects of self-administered heroin and causing less respiratory depression than do full agonist opioids, thus affording protection from heroin overdose.[34,35]

An association between the expansion of buprenorphine treatment and the decline in heroin overdose deaths was also found in France,[15] where primary care physicians provide buprenorphine treatment without a special licensing requirement in the context of a public health system that allowed a significant expansion of access to opioid agonist treatment during this period. From 1995 to 1999 the number of patients receiving opioid agonist treatment in France increased from less than 2000 to more than 60 000 per year (80% on buprenorphine and 20% on methadone), whereas the number of opioid overdose deaths declined 79% from 465 to 120.[15]

Previous research has shown that methadone treatment reduces heroin overdose mortality.[17,36–38] Numerous factors may have masked an effect of methadone expansion in our study, including the short time frame of the investigation and the sharp rise in heroin purity between 1995 and 1999, which is generally correlated with increased heroin availability. Buprenorphine may have had an accidental advantage over methadone in our analysis because it became available only in the latter half of the period under investigation, when heroin purity was generally stable or declining, whereas methadone treatment was continuously available in the community. We cannot discount the possibility that the observed relationship between the decrease in heroin overdose deaths and the expansion of buprenorphine treatment is coincidental and that other unmeasured factors occurring contemporaneously with the expansion of buprenorphine treatment were contributing to the reduction in overdose deaths. For example, reductions in patterns of arrest and release after brief periods of incarceration might also influence risk of overdose death. Nevertheless, simple visual inspection of the trend lines shows what appears to be a clear inverse relationship between heroin overdose deaths and expansion of buprenorphine treatment. It is also important to note that isolating the unique effects of methadone and buprenorphine is difficult because expansion of both occurred in parallel and increased the number of patients receiving opioid agonist treatment overall.

Heroin is the major drug of abuse in Baltimore City, and thus heroin-associated mortality was our primary focus. There was an increase in cases of methadone-associated mortality during the period of methadone treatment expansion, and it is possible that some of the methadone-associated deaths were a consequence of this expansion. However, we did not confirm a direct link between changes in methadone overdose and methadone treatment expansion in a time series analysis. Furthermore, during this time there was a larger national trend of increasing methadone-associated mortality, which was driven primary by increased prescribing of methadone for pain management rather than addiction treatment.[32,33] Nevertheless, it has been reported that expanding methadone treatment in settings outside the United States where methadone maintenance is provided without direct administration of doses can result in some increase in methadone-associated mortality.[39] In the United States, where most methadone doses are administered under direct observation, the positive public health benefits of expanding such treatment outweigh the unintended consequences of methadone overdose.

The potential unintended public health consequences of medication treatment expansion are minimized in the case of buprenorphine because of its distinct pharmacology. As a partial opioid agonist, buprenorphine has a dose–effect ceiling on respiratory depression.[35] Although buprenorphine-associated deaths have been reported in the literature when accompanied by benzodiazepine injection, death attributable to buprenorphine alone is uncommon.[40,41]

The purity of heroin the DEA seized in Baltimore has varied over the years. Although there were several years in which overdoses increased as mean heroin purity increased, when considered over the entire 1995–2009 period, there was not a statistically significant relationship between these increases in purity and the number of heroin overdose deaths. Other research has found a positive relationship between heroin purity and overdose deaths.[42] The number of Baltimore street heroin samples analyzed annually ranged from 14 to 33. It is possible that these seizures are not adequately representative of the purity of heroin on the streets. It is also possible that variability in heroin purity may affect risk of overdose death as much as or more than the average purity for a given year. Indeed, in several years, the purity of individual samples ranged from 2.5% to greater than 90%. Despite this wide variability in purity that persisted at least through 2008, the increase in opioid agonist treatment appears to have ameliorated the effects of spikes in purity in particular samples.

An alternative explanation for the decrease in overdose deaths is the population decline in Baltimore City during the period in question. However, according to US Censuses, the Baltimore City population declined less than 5% between 2000 and 2010, making this an unlikely explanation for our findings, unless there was a disproportionately greater migration of drug opioid–addicted individuals from Baltimore City.

Limitations

There are several limitations to our investigation. First, the number of buprenorphine

patients was an estimate and, unlike the number of methadone patients, the exact count of unique patients treated annually is not known with absolute certainty. However, we believe that the estimation methodology provides a good approximation of actual numbers of patients treated with buprenorphine.

Second, treatment retention patterns for the methadone and buprenorphine patients are not known and might vary from year to year and between medications. Data on person-years in treatment was not available, and thus we used the number of unique patients treated each year as an indicator of the ecological penetration of methadone and buprenorphine. Third, it is quite possible that the count of some unknown number of patients is duplicative in a given year, as patients could have been in both methadone treatment and buprenorphine treatment during a single year.

Fourth, the impact of diverted street methadone and buprenorphine in reducing heroin overdoses is not known. Prior reports indicate that although both of these medications have abuse potential, they are most often used by out-of-treatment individuals to self-medicate symptoms of heroin withdrawal.[43–45] Fifth, we did not know the number of heroin-using adults in the city over the period with certainty, and it may have declined as a result in changes in incidence, recovery, incarceration, death, and natural epidemiologic cycles. Similarly, other trends that may have affected heroin use in Baltimore include a possible increase in the use of prescription opioids[46] and a possible change in the route of heroin use from injection to snorting.[47,48]

Sixth, from an analytic standpoint, 15 years of data represent a short time series that offers limited statistical power to detect relationships. Seventh, it is possible that some of the observed decrease in overdose deaths mirrors larger mortality trends. For example, overall death rates in Baltimore steadily declined by 31.3% from 1995 to 2009,[49] whereas homicide rates declined by 26.1% during the same period,[50] with the bulk of the decrease occurring from 1995 to 2000. By comparison, the decline in overdose deaths from 1995 to 2009 was even more robust at 51.8%.

Finally, there were several other programs initiated in Baltimore during the period we studied that could have had some influence on heroin overdose deaths, although the number of individuals served in these programs was relatively modest compared with the number of patients receiving opioid agonist treatment. These programs included an overdose prevention initiative[51,52] that distributed about 300 vials a year of naloxone beginning in 2004 and a small methadone program in the Baltimore City jail for incarcerated patients who were treated with methadone in the community beginning in 2008. The extent to which any or a combination of these initiatives may have affected heroin overdose deaths in Baltimore above and beyond the introduction of buprenorphine treatment, the expansion of methadone treatment, and shifts in heroin purity is not known.

Conclusions

Despite these limitations, our findings indicate that increased access to opioid agonist treatment of heroin addiction in Baltimore—particularly expansion of buprenorphine treatment—may have significantly contributed to the reduction in heroin overdose deaths. This is consistent with the experience with buprenorphine treatment in France.[15] Increased access to methadone treatment may have also played a role once the combined number of methadone and buprenorphine patients reached some critical level. Although we have demonstrated that increasing ecological penetration of opioid agonist treatments was associated with decreasing overdose mortality, future research should assess disparities in treatment penetration and their association to mortality. Our findings suggest that jurisdictions have the potential to reduce heroin overdose deaths through policies that support the expansion of evidence-based medication treatment of opiate dependence. ■

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Contributors

R. P. Schwartz developed the study concept, acquired the data, interpreted the analysis, and drafted the article. R. P. Schwartz, J. Gryczynski, and K. E. O'Grady were responsible for the integrity of the data and the accuracy of the data analysis. J. Gryczynski conducted the data analysis and drafted the Methods section. K. E. O'Grady contributed to the study design, revised the Methods section, and supervised the data analysis. J. M. Sharfstein made substantial contributions to the acquisition of the data and helped revise the article. G. Warren, Y. Olsen, and S. G. Mitchell contributed to the interpretation of the data and revision of the article. J. H. Jaffe made substantial contributions to the study's conception and critically revised the article. All authors approved the final version of the article.

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Human Participant Protection

Because this study used archival data that were not identifiable and therefore did not have human participants, no protocol approval was necessary.

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