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Examination of methadone involved overdoses during the COVID-19 pandemic☆

Daniel E. Kaufman [a], Amy L. Kennalley [b], Kenneth L. McCall [c,d], Brian J. Piper [a,e,*,1]

[a] Touro College of Osteopathic Medicine, Middletown, NY, USA
[b] Geisinger Commonwealth School of Medicine, Scranton, PA, USA
[c] University of New England, Portland, ME, USA
[d] Binghamton University, NY, USA
[e] Center for Pharmacy Innovation and Outcomes, Forty Fort, PA, USA

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ABSTRACT

Background: The US opioid overdose epidemic continues to escalate. The restrictions on methadone availability including take-home dosing were loosened during the COVID-19 pandemic although there have been concerns about the high street value of diverted methadone. This report examined how fatal overdoses involving methadone have changed over the past two-decades including during the pandemic.
Methods: The CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) was used to find the unintentional methadone related overdose death rate from 1999 to 2020. Unintentional methadone deaths were defined using the ICD X40–44 codes with only data for methadone (T40.3). Data from the DEA's Automation of Reports and Consolidated Orders System (ARCOS) on methadone overall use, opioid treatment programs use, and pain management use was gathered for all states for 2020 and corrected for population.
Results: There have been dynamic changes over the past two-decades in methadone overdoses. Overdoses increased from 1999 (0.9/million) to 2007 (15.9) and declined until 2019 (6.5). Overdoses in 2020 (9.6) were 48.1% higher than in 2019 ($t(50) = 3.05$, $p < .005$). The state level correlations between overall methadone use ($r(49) = +0.75$, $p < .001$), and opioid treatment program use ($r(49) = +0.77$, $p < .001$) with overdoses were positive, strong, and statistically significant. However, methadone use for pain treatment was not associated with methadone overdoses ($r(49) = -0.08$).
Conclusions: Overdoses involving methadone significantly increased by 48.1% in 2020 relative to 2019. Policy changes that were implemented following the COVID-19 pandemic involving methadone take-homes may warrant further study before they are made permanent.

1. Introduction

The United States (US) is in the midst of an opioid overdose epidemic that has spanned over two decades and continues to escalate [1]. Methadone is long-acting mu receptor full opioid agonist approved to treat opioid use disorder (OUD) and for pain management. Methadone maintenance treatment reduces the illicit use of heroin, death rates and criminality associated with heroin use, and allows patients to improve their health and social productivity [2]. Among opioids classified as Schedule II and III, analysis of the Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS) comprehensive database by morphine mg equivalents revealed that methadone was by far the predominant opioid in the US [3]. However, there was considerable variation in the availability of methadone with some states (WY, SD, NE, MS) having less than two methadone dispensing opioid treatment program (OTP) facilities per million residents [4]. Retention in OUD treatment has repeatedly been demonstrated to be greater with methadone than with buprenorphine [5–7]. However, observational research has found that chronic methadone was associated with an

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* Corresponding author at: Touro College of Osteopathic Medicine, Middletown, NY, USA.
E-mail addresses: psy391@gmail.com, bpiper@som.geisinger.edu (B.J. Piper).
[1] Department of Medical Education, Geisinger Commonwealth School of Medicine, 525 Pine Street, Scranton, PA 18509

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elevated body mass index [8]. Methadone induced respiratory depression and cardiac abnormalities may also lead to mortality [9–11]. The street price per mg of methadone ($0.96) was equivalent to oxycodone ($0.97) although reports for the latter were twenty-fold more common [12]. There was a 17-fold individual difference in methadone concentrations for a given dose which was largely due to genetic variation in the CYP3A4 enzyme [13]. Distribution of methadone for pain declined 35% between 2017 and 2019 [4].

The policies for US healthcare providers prescribing treatments for OUD are generally recognized as more restrictive than those for other controlled substances like oxycodone or fentanyl. The restrictions on methadone availability including take-home dosing were relaxed in March of 2020 to accommodate the COVID-19 pandemic. Individual treatment facilities could elect whether to make greater use of telemedicine and provide a two-week methadone supply for less stable patients and a four-week supply of take-homes for stable patients [14]. While many patients have understandably been enthusiastic about this change [15–17], this development may also be concerning. The introduction of supervised dosing of methadone in England and Scotland was associated with a pronounced reduction in deaths due to methadone overdose [18]. Calls involving methadone to poison control centers increased 5.3% during the pandemic [19]. One of the most pressing questions in addiction medicine is how be responsive to both the overdose crisis and COVID-19 pandemic including maximizing the availability of life-saving medications while also protecting public safety. Therefore, this report: 1) examined how fatal methadone overdoses have changed over the past two-decades including following the pandemic, and 2) evaluated whether there was any correlation at a state-level between methadone distribution patterns and methadone overdoses.

2. Materials methods

2.1. Procedures

The Center for Disease Control and Prevention's (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) database which draws data from death certificates was used for this cross-sectional study to find the unintentional methadone related overdose death rate from 1999 to 2020 [20]. Unintentional methadone deaths were defined using the International Statistical Classification of Diseases (ICD), 10th revision codes: X40–44 with only data which was coded for methadone (T40.3). This includes polydrug deaths involving other substances in addition to methadone [21]. States with overdoses that were so low that results were suppressed (32.5% of values), were coded as 0. WONDER has been employed in much prior overdose research [21,22]. Data from the Drug Enforcement Administration's ARCOS database on methadone overall distribution, opioid treatment programs (OTP, note that the DEA uses "narcotic treatment program" in the ARCOS reports) use, and pain management (including pharmacies, hospitals, and mid-level practitioners) use was gathered for all states and Washington DC for 2020 and corrected for population according to the US Census. ARCOS is a comprehensive database for drug distribution. ARCOS showed very high correspondence with state prescription drug monitoring programs (e.g. r = 0.985 for oxycodone) [22,23]. ARCOS reports on the 1726 OTPs that is not covered by another data source [24]. Procedures were approved as exempt by the University of New England IRB. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed [25].

2.2. Data-analysis

Statistics (e.g. a Pearson correlation between overdoses and population corrected distribution) were completed with Systat with

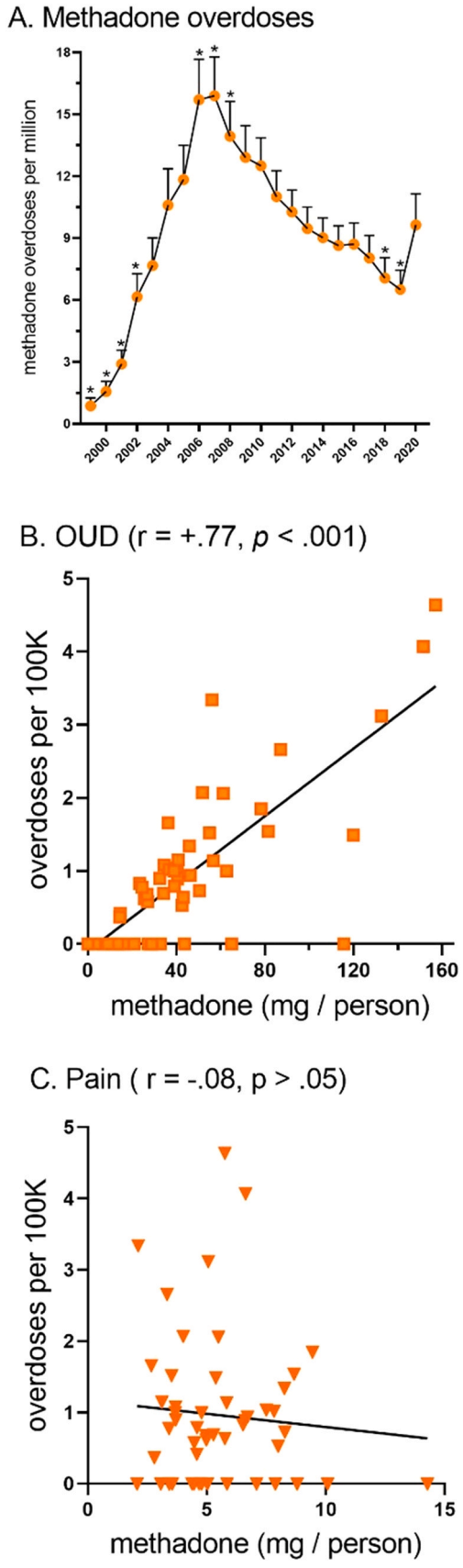

Fig. 1. Dynamic changes in methadone overdoses as reported to the Center for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (WONDER) database (A, * p < .05 versus 2020). Correlations between per capita methadone distribution for Opioid Use Disorder (OUD, B) and pain (C) treatment in 2020 as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS).

Table 1
States ranked for methadone involved overdose deaths per 100,000 population in 2020 as reported to the Center for Disease Control and Prevention's (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER). Sixteen states (Alaska, Arkansas, Hawaii, Iowa, Idaho, Kansas, Mississippi, Montana, Nebraska, New Hampshire, North Dakota, Oklahoma, South Dakota, Utah, Vermont, and Wyoming) did not report any methadone overdoses. DC: District of Columbia.

Rank	State	Overdoses	Rank	State	Overdoses
1	Rhode Island	4.64	19	Arizona	1.00
2	Washington DC	4.07	20	Virginia	1.00
3	Delaware	3.34	21	Kentucky	0.94
4	Connecticut	3.12	22	Minnesota	0.90
5	New Mexico	2.66	23	North Carolina	0.89
6	West Virginia	2.07	24	Florida	0.83
7	New York	2.06	25	South Carolina	0.79
8	Maine	1.85	26	Tennessee	0.78
9	Illinois	1.66	27	Oregon	0.73
10	Massachusetts	1.54	28	Georgia	0.69
11	New Jersey	1.52	29	Ohio	0.68
12	Maryland	1.49	30	Indiana	0.64
13	Washington	1.34	31	California	0.62
14	Wisconsin	1.15	32	Louisiana	0.58
15	Pennsylvania	1.14	33	Alabama	0.53
16	Colorado	1.08	34	Missouri	0.42
17	Michigan	1.04	35	Texas	0.37
18	Nevada	1.02			

$p < .05$ considered statistically significant. Figures were generated with GraphPad Prism.

3. Results

There have been dynamic changes over the past two-decades in methadone overdoses. Overdoses increased from 1999 throughout the early 2000 s, peaked in 2007, and declined until 2019. Overdoses in 2020 were 48.1% higher than in 2019 ($t(50) = 3.05$, $p < .005$, Fig. 1A). Overdoses in 2020 were also significantly elevated relative to 2000–2003 and 2018 but significantly lower than 2006–2008. Among the top ten states for overdoses in 2020, nine (Rhode Island, Washington DC, Delaware, Connecticut, West Virginia, New York, Maine, Illinois, and New Hampshire) were located in the eastern US (Table 1).

The correlations between overall methadone distribution ($r(49) = +0.75$, $p < .001$, not shown), and OTP distribution ($r(49) = +0.77$, $p < .001$, Fig. 1B) with methadone overdoses in 2020 was positive, strong, and statistically significant. However, methadone for pain treatment was not associated with methadone overdoses (Fig. 1C).

There was a moderate correlation between overall methadone distribution ($r(49) = +0.44$, $p < .001$), pain treatment ($r(49) = +.47$, $p < .0005$) with methadone overdoses in 2007, the peak year of overdose, but not with OTP use ($r(49) = +0.22$, $p = .13$). There were no significant correlations ($p > .24$) between overdoses and distribution in 2019.

4. Discussion

The key finding from this report was that methadone overdoses significantly increased by 48.1% in 2020 relative to 2019. This increase is consistent with but also much larger than the 5.3% elevation in calls involving methadone reported nationally to poison control centers in the year following the March 16, 2020 relaxation of methadone take-home regulations [14,19]. Facilities providing methadone could also accommodate the COVID-19 pandemic by reducing or eliminating their in-person counseling practices and urine toxicology screens. It would be difficult to overstate the vehemently critical attitudes toward limited access to methadone take-homes pre-pandemic [16]. Qualitative research has determined that OUD patients have been enthusiastic about their expansion [15,17]. However, a study of twenty providers in New Jersey revealed that they were more nuanced with all desiring that the COVID-19 policy changes be made permanent while some also expressing concerns about limited drug urine samples collected and a subset expecting that their practice would become more similar to the pre-pandemic period [26]. Importantly, a finding of an increased rate of methadone involved overdoses following relaxation of supervised administration is consistent with an earlier policy report that determined that the introduction of supervised methadone administration by community pharmacists was associated with a major reduction in deaths due to methadone overdoses [18].

There were over four-hundred thousand patients receiving methadone for OUD in the US in 2019 [27]. However, the recent elevation in overdoses involving methadone was not due to greater methadone prescribing because there were only 311,531 (i.e. an 23.7% decrease relative to 2019) patients receiving methadone in 2020 [27]. Although eastern and particularly northeastern states had the most methadone overdoses, the rate in the highest state (Rhode Island = 4.6 / 100,000 or 1 per 21,739) was still low and attests of the overall safety of methadone, especially when used as prescribed. The chief medical examiner in Vermont found that the methadone was obtained through diversion in two-thirds (67%) of the methadone-related fatalities and three-fifths (62%) involved another substance [28]. National methadone overdoses in 2020 were also significantly lower than their peak (2006–2008) which is congruent with and extends upon reports covering earlier time-frames [10,29]. The Food and Drug Administration issued an advisory in November of 2006 cautioning about the potential for death, overdose, and serious cardiac arrhythmias associated with methadone [30] and there was a voluntary manufacturer restriction in January of 2008 on the 40 mg formulation of methadone [29]. Similar to most other Schedule II opioids [3], the distribution of methadone for pain has undergone substantial declines from 2016 to 2019 [4] which would limit the amount available for potential diversion [12]. The increased use of genotyping for CYP3A4 and other liver enzymes could improve the safety profile of methadone [13]. Interestingly, the number of patients receiving methadone for OUD also decreased by almost one-quarter (23.7%) between 2019 (408,550) and 2020 (311,531) [27]. A prior report examined the ratio of methadone overdoses and poison control calls relative to the "low" rate of prescriptions [31] but the authors were apparently unaware that their data source (IMS Health, now IQVIA) [23] did not include methadone when administered from OTPs [32]. We hope that these findings will not add to further misconceptions about the safety of methadone relative to other less widely prescribed Schedule II opioids [3]. It is also important to contrast our findings with those of another recent brief report that used a complementary overdose database and found that methadone overdoses increased 94.1% following the March, 2020 policy change while those not involving methadone increased by 78.1% [33]. In evaluating whether our findings contradict or extend upon those of others [33], it is crucial to appreciate that the doubling of the raw (i.e. uncorrected for changing prescriptions or methadone patients) methadone overdoses occurred when the volume of methadone distributed to opioid treatment programs was stable (−0.1%) [34] but, as noted previously, the number of patients receiving methadone in federally regulated opioid treatment programs from 2019 to 2020 underwent a sizable decline (−23.7%) [27]. These results also complement those from another recent study with WONDER [21] that found that, relative to US overdose deaths without methadone from April 2020 to March 2021, overdose deaths involving methadone were more likely among females (40.4% vs. 30.2%), more likely to involve benzodiazepines (25.8% vs 12.5%), but less likely to involve non-methadone synthetic opioids (45.2% vs 64.1%), or psychostimulants (16.2% vs 27.6%) [21].

This report also took advantage of the tremendous variation in methadone distribution at a state level [4] to test if there were any

associations with methadone overdoses. There was a strong correlation (r = +.77) between the population corrected distribution of methadone for OUD and methadone overdoses. Importantly, there was no significant relationship (r = −.08) between the distribution of methadone for pain with overdoses. There are at least three viable interpretations of the present descriptive pharmacoepidemiological findings. First, the COVID-19 policy changes [14] could be viewed as resulting in a quasi-experimental design and the administration of methadone for OUD via telemedicine may have increased the risk for diversion of this respiratory depressant resulting in more methadone involved overdoses. As several policies (increased take-homes, reduced urine-analysis, and decreased in-person individual and group counseling sessions) were implemented simultaneously, it would be premature to attribute any change in mortality to a single policy change. A second possibility is that another policy confound accounted for the increase in overdoses. New patients could receive buprenorphine, but not methadone, via telemedicine [14]. As a Cochrane review concluded that methadone was superior to buprenorphine in retaining patients in treatment [7], the greater buprenorphine availability by any primary care provider with an X-waiver may have resulted in an increase in only the most severe/high risk OUD starting methadone during a stressful period of reduced social connections due to isolation combined with economic uncertainty. The third possibility is that due to methadone's long half-life [13], this substance was being increasingly preferentially listed on death certificates instead of more rapidly eliminated, or more obscure (e.g. xylazine, novel fentanyl analogues, novel benzodiazepines) substances [34,35] which may not be being routinely assessed with analytical chemistry due to fiscal considerations. Concerns about the non-homogeneity for the death determination process are available elsewhere [20,36] and are an important caveat of the WONDER results. The present data, in conjunction with that of others [18,33] contributes to evidence about both the benefits and harms of methadone and the need to be clear eyed about the potential consequences of any decreased regulation.

In conclusion, this study identified a pronounced (48%) increase in methadone overdoses in the US during the COVID-19 pandemic. As there was a high state-level correspondence between the quantities of methadone distributed for OUD and methadone overdose deaths, some caution and further study may be warranted before making all the COVID-19 accommodations permanent.

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CRediT authorship contribution statement

Daniel Kaufman: Conceptualization, Formal analysis, Investigation, Writing – original draft. **Amy Kennalley**: Data curation, Visualization, Writing – original draft. **Kenneth McCall:** Project administration, Writing – review & editing. **Brian Piper**: Conceptualization, Methodology, Supervision, Writing – review & editing. All authors approved the final version.

Declaration of Interests

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