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A comparison of blood toxicology in fatalities involving alcohol and other drugs in patients with an opioid use disorder treated with methadone, buprenorphine, and implant naltrexone

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ABSTRACT

Background: Methadone, buprenorphine, and implant naltrexone have comparable efficacy in preventing death from drug intoxication during treatment, but there may be differences between treatments in the specific drugs contributing to death and in the risk of death during different phases of treatment.

Objective: The objective of this study was to compare concentrations of individual drugs in decedents for evidence that the three medications use to treat opioid use disorders differed in the protection they offered against fatal overdose.

Methods: Fatalities with a primary or co-diagnosis of alcohol or other drug poisoning in patients treated with methadone (n = 66, 74.2% male), buprenorphine (n = 54, 74.1% male), or naltrexone (n = 28, 85.7% male) were identified by combining treatment (Monitoring of Drugs of Dependence System and clinical records) and mortality records (Western Australian Death Registry). Quantitative postmortem blood drug analysis data were obtained for drug-related deaths. The presence/absence of drugs were compared between the three medication groups and between phases of treatment (on-treatment/off-treatment).

Results: Opioids (89.8%) and benzodiazepines (76.2%) were most commonly identified in post-mortem blood. The three medication groups did not differ materially in the drugs present postmortem, except that alcohol was less prevalent in naltrexone-treated cases. Morphine or heroin intoxication was implicated in more patients dying off-treatment than on-treatment but levels of morphine and other drugs were comparable across the two phases.

Conclusion: Comparisons of postmortem concentrations of specific drugs indicated that patients treated with methadone, buprenorphine, and implant naltrexone had comparable susceptibilities to lethal co-intoxication and that similar drug mixtures contributed to death.

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KEYWORDS

Buprenorphine; methadone; mortality; naltrexone; overdose; toxicology

Introduction

Opioid use disorders (OUD) are associated with increased morbidity and mortality, with overdose and poisoning contributing significantly. In patients with an OUD, overdose is the commonest cause of death, with pooled estimates for overdose mortality of 6.2 deaths per 1,000 patient years (ptpy) (1). Non-fatal overdoses outnumber fatal overdose by more than 20-fold (2,3).

Although the term ‘overdose’ implies an excessive dose, postmortem concentrations of morphine in cases of heroin overdose death overlap the range found in opioid users who have died from other causes, such as traffic accidents or homicide (4–6). Most overdose deaths among opioid users involve changes in tolerance or the co-administration of other drugs. Tolerance builds quickly after sustained opioid use, leading to escalating doses, then wanes when opioids are ceased. Failure to compensate for lost tolerance contributes substantially to opioid mortality following release from incarceration or inpatient rehabilitation (7,8). The use of other drugs is common in patients with an opioid use disorder (9,10). Alcohol and benzodiazepines, particularly, amplify the risk of opioid-induced respiratory depression (11). In a study of 192 fatal opioid overdoses, alcohol and benzodiazepines were present in 61.5% and 40.1%, respectively (12). Morphone-tolerant mice have shown an unanticipated sensitivity to alcohol-induced respiratory depression,
implying that opioid tolerance may not translate to tolerance for alcohol – morphine mixtures (13).

Pharmacotherapies for opioid use disorders reduce mortality, however, drug poisonings remain common. The opioid agonist therapeutics, methadone, and buprenorphine, may themselves contribute to poisoning (14–16). Some phases of therapy carry particular poisoning risk. Opioid overdose is high in patients entering and exiting methadone therapy and in oral naltrexone patients following the cessation of treatment. However, little is known about how these therapies compare in terms of the type and amount of co-intoxicants involved in deaths occurring while on treatment, off treatment and in high-risk transition periods. We have observed these time-treatment interactions in earlier studies (17) and noted that there were also differences in the specific drugs present in decedents from methadone, buprenorphine, and implant naltrexone programs.

For this study, we set out to further explore the toxicological circumstances of death in these three patient populations, drawn from the same community but entering different treatment programs. We had particular concern to compare concentrations of individual drugs between the three populations and between phases of treatment, so as to reveal differences that denoted different susceptibilities. Separating and measuring the mortality risks that arise from the pharmacotherapy itself and from failure of pharmacotherapy is assisted substantially by quantitative postmortem toxicology, but still needs guidance from postmortem examination findings and the circumstance surrounding the death. We combined this information to test interactions between the three opioid pharmacotherapies, co-intoxicants and phases of treatment.

**Methods**

**Patients**

Patients with an opioid use disorder over 18 years old, treated with methadone (n = 3,515; 19,462 years of follow-up), buprenorphine (n = 3,250; 14,715 years) or implant naltrexone (n = 1461; 7,011 years) for the first time between January 2001 and December 2010 in Western Australia (WA) were studied. Following their first treatment, patient frequently moved between treatments, and on and off treatments. Methadone and buprenorphine patients were obtained from the Monitoring of Drugs of Dependence System (MODDS), which is maintained by the state Department of Health to store records relating to the Community Program for Opioid Pharmacotherapy. In Australia, methadone and buprenorphine are generally dispensed daily from community pharmacists. Methadone and buprenorphine dosing reports are collected into the MODDS from authorized participating pharmacies statewide. Patients treated with implant naltrexone were taken from treatment lists of a community drug and alcohol clinic, which was the sole provider of implant naltrexone during this period.

**Treatment data**

Data from the MODDS revealed if a patient was on treatment during a given month. Consecutive months were compiled to form treatment periods. To locate approximate start and end dates, the data were matched against the Authorization Database, which provided the first date for which the patient was authorized to receive the treatment and the date treatment was ceased. If an exact start date was not available, the 15th of the month was used as a start date unless the patient died before this time, in which case the 1st of the month was used. The last day of the month was used as the termination date where an exact date was unavailable. In two fatalities, methadone was present at therapeutic blood concentrations postmortem, but the treatment data suggested that the decedents only received 1 day of treatment in the week preceding death. It was deemed most likely that these patients were, in fact, still on treatment at the time of death.

For patients treated with implant naltrexone, the date of treatment was provided by the clinic. A single treatment was taken to provide therapeutic levels of naltrexone for 182 days, as evidenced by efficacy and pharmacokinetic data (18–20). A shorter period was adopted for patients who transitioned onto methadone or buprenorphine between 121 and 181 days, reasoning that the need to transition reflected a loss of naltrexone efficacy. Interpatient variability in implant naltrexone pharmacokinetics might have been responsible in such cases.

**Data linkage**

Patients were linked by the WA Data Linkage Branch (DLB) with the WA Death Registry. Fatalities involving alcohol or other drugs were identified through International Classification of Diseases and Related Health Problems, Revision 10 (ICD-10) codes (T36-T51) and extracted from the data sets. Death registrations that also included text fields were individually examined for a reference to alcohol or other drugs. Postmortem toxicology reports for these cases were then extracted from the records of Chemistry Center of Western Australia, which is responsible for toxicological testing in all cases referred by the State Coroner for postmortem
examination. Coroners’ determinations of cause of death were extracted for all cases. Data were de-identified by the DLB and provided to the research team.

**Mortality and toxicity**

The study group comprised 5,646 patients (65.8% male), among whom 317 deaths (71.6% male) occurred over an average follow up of 7.3 years. Three fatalities were excluded because they were registered to more than one opioid pharmacotherapy at the time of death. Of the 314 remaining deaths, 148 had a primary or co-diagnosis of alcohol or other drug poisoning (76.4% male), including 66 methadone (74.2% male), 54 buprenorphine (74.1% male), and 28 naltrexone (85.7% male). Demographics and cause-specific mortality rates have been previously published (17). Patients were allocated to a treatment group based on their most recent treatment.

Postmortem toxicological analysis was standard for all coronial autopsies. Results were available for all cases, except one from the methadone group whose death was attributed to accidental methadone toxicity in the Coroner’s determination. Liver was the only available analytical medium for four cases (2 methadone, 1 buprenorphine, and 1 naltrexone), where advanced decomposition made blood unavailable. For the remaining 143 cases, blood specimens were collected at the time of mortuary admission and/or at postmortem examination. The lower limits of quantitation for individual drugs allowed confident detection of toxicologically relevant concentrations, with the exception of the highly potent opioids buprenorphine and fentanyl. For those drugs, toxicity may be experienced at blood concentrations below the commonly employed limit of detection of <5 μg/L (<0.005 mg/L) (21,22). Targeted analysis, to greater sensitivity, was available when surrounding evidence suggested that buprenorphine or fentanyl might be present.

The standard procedure for toxicological analysis was an initial screen by immunological or chromatographic methods for a broad range of drugs of forensic interest, followed by quantitation using specific chromatographic and mass spectrometric techniques. Quantitative analyses were carried out on mortuary admission peripheral blood specimens and/or blood collected from a peripheral vessel (most commonly a femoral or subclavian vessel) at postmortem examination, as far as volume availability allowed. This minimizes the influence of postmortem drug redistribution on measured drug concentration. Where quantitative analyses of blood specimens from different sites yielded differing drug concentrations, the mortuary admission peripheral or postmortem peripheral blood concentrations were adopted for interpretation, in preference to central vessel specimens, which are potentially more affected by postmortem drug redistribution.

Causes of death were initially judged by the forensic pathologist, based on ante-mortem history, scene evidence, postmortem examination findings, postmortem toxicology, and other investigations. They were then reviewed by an experienced forensic toxicologist to judge whether the toxicological evidence supported the drugs’ proposed contribution to causation, in a manner consistent with the guidelines of the National Association of Medical Examiners and American College of Medical Toxicology Expert Panel on Evaluating and Reporting Opioid Deaths (23). Opinions were concordant in all cases, with differences only in relative importance attributed to individual drugs in a minority of multi-drug deaths.

Cases with morphine present were further examined for information about recent use of morphine, codeine, and heroin. The detection of morphine, without any codeine, was taken as evidence that a medicinal morphine preparation had been taken. Detection of monoacetylemophine in blood or urine provides unambiguous confirmation of heroin use. However, monoacetylmorphine is cleared very rapidly from blood, so is an insensitive index when death has been delayed or postmortem blood collection is delayed (24). The time-dependent change in the ratio of unconjugated (free) morphine to its glucuronide conjugates does provide a more sensitive, but less specific, indication whether death closely followed the use of morphine or heroin. Those ratiometric criteria were validated at a time when heroin was the dominant opioid drug of abuse and have become less useful in an era when abuse of diverted medicinal morphine is common. Additionally, the long persistence of morphine conjugates make the criteria unreliable in repeatedly-dosing heroin or morphine users. For the cases in this study, therefore, recent heroin use was inferred from the presence of monoacetylmorphine, from the morphine-codeine ratio or through a forensic pathologist’s determination, based on surrounding evidence. Ante-mortem blood was available for analysis in a few cases.

A coroner’s determination of suicide was accepted.

**Statistical analysis**

Fatalities were categorized according to their most recent opioid pharmacotherapy, then separated further according to whether death occurred while the patient was on treatment or was off/post-treatment. For methadone, the first 28 days on treatment were also examined.
as potentially being a time of special vulnerability to opioid overdoses (25). This was not possible for buprenorphine and naltrexone as there were no opioid overdoses identified in the first 28 days of treatment. Median concentrations and ranges were calculated for individual drugs and compared across treatment groups and phases of treatment. The percentage of deaths involving each drug type were also compared between treatment types and phases, as were the percentages of decedents with common drug combinations, for example, opioids with benzodiazepines.

**Ethics**

This study protocol was reviewed and approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).

**Results**

**Study population and causes of death**

Drug toxicity was judged to be a cause of death or a contributor to death in 148 of the total 314 deaths in the study population, based on circumstances of death, postmortem examination findings and blood or liver toxicology. These represented 66/158 (41.8%), 54/106 (50.9%) and 28/50 (56.0%) of total deaths in the methadone, buprenorphine and naltrexone groups, respectively. These were not significantly different between the three treatment groups. Comprehensive toxicology results were available for 147 of the 148 cases. Three deaths were attributed primarily to carbon monoxide poisoning, sharp injury and drowning, with a drug contribution deemed also present in all. Fourteen cases died by suicide. Drug intoxication was the principal cause of death in all but one of the suicide cases.

Opioid drugs were the most common drugs, with presence in 132 of the 147 (89.8%) deaths (Figure 1). Only a few of these (14.4% of all deaths involving opioids; Table 1) were opioids the only drugs. Of these, 42.1% were linked to heroin or morphine exposure, while 31.6% were the result of methadone toxicity. Benzodiazepines were present in the majority (77.3%) of opioid-related deaths. In approximately a quarter of opioid deaths, alcohol (24.2%), amphetamines/methamphetamines (25.8%) or tetrahydrocannabinol (THC) (22.7%) were present. In non-opioid drug cases, benzodiazepines were again the most common

**Figure 1.** Drugs commonly detected in deceased patients treated with methadone, buprenorphine, and naltrexone whose death has been associated with alcohol and other drugs (AOD).
Table 1. Combinations of drugs found at postmortem in methadone, buprenorphine and naltrexone patients who had died of poisoning.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids alone</td>
<td>9.2%</td>
<td>13.0%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Opioids + benzodiazepines</td>
<td>72.3%</td>
<td>68.5%</td>
<td>64.3%</td>
</tr>
<tr>
<td>Opioids + alcohol</td>
<td>29.2%</td>
<td>18.5%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Opioids + meth/amphetamines</td>
<td>13.8%</td>
<td>25.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Opioid + THC</td>
<td>26.2%</td>
<td>22.2%</td>
<td>17.9%</td>
</tr>
<tr>
<td>Non-opioids</td>
<td>12.3%</td>
<td>11.1%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

THC = tetrahydrocannabinol

*Absence of benzodiazepines, alcohol, amphetamine, methamphetamines or THC. Other drugs, particularly medications at therapeutic and sub-therapeutic doses, may have been present.

Table 2. Drugs most commonly identified in deaths of patients with an opioid use disorder treated with methadone, buprenorphine or implant naltrexone, including percentage of drug-related deaths involving each drug and median (range) blood levels of each drug.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Methadone (n = 65)</th>
<th>Buprenorphine (n = 54)</th>
<th>Naltrexone (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid</td>
<td>87.7% (57)</td>
<td>88.9% (48)</td>
<td>96.4% (27)</td>
</tr>
<tr>
<td>- Morphine (total)</td>
<td>53.8% (35)</td>
<td>61.1% (33)</td>
<td>88.9% (48)</td>
</tr>
<tr>
<td>- Morphine (free)</td>
<td>49.2% (32)</td>
<td>59.3% (32)</td>
<td>67.9% (19)</td>
</tr>
<tr>
<td>- Heroin</td>
<td>32.3% (21)</td>
<td>42.6% (23)</td>
<td>53.6% (15)</td>
</tr>
<tr>
<td>- Methadone</td>
<td>38.5% (25)</td>
<td>11.1%** (6)</td>
<td>21.4% (6)</td>
</tr>
<tr>
<td>Oxycodone, buprenorphine</td>
<td>15.4% (10)</td>
<td>16.7% (9)</td>
<td>17.9% (5)</td>
</tr>
<tr>
<td>- Alcohol</td>
<td>35.4% (23)</td>
<td>22.2% (12)</td>
<td>10.7%* (3)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>76.9% (50)</td>
<td>79.6% (43)</td>
<td>67.9% (19)</td>
</tr>
<tr>
<td>- Diazepam</td>
<td>70.8% (46)</td>
<td>75.9% (41)</td>
<td>60.7% (17)</td>
</tr>
<tr>
<td>- Alprazol</td>
<td>13.8% (9)</td>
<td>9.3% (5)</td>
<td>28.6% (8)</td>
</tr>
<tr>
<td>THC</td>
<td>29.2% (19)</td>
<td>18.5% (10)</td>
<td>21.4% (6)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>15.4% (10)</td>
<td>24.1% (13)</td>
<td>21.4% (6)</td>
</tr>
</tbody>
</table>

* p < .05, ** p < .001

THC = tetrahydrocannabinol

Liver tissue only was available for analysis for three cases where morphine was detected.

Drug concentrations in blood, so excluding the four patients where only liver was available for analysis. Drug concentrations are expressed in milligrams per liter (mg/L), except alcohol, which is expressed in grams per deciliter (%) and tetrahydrocannabinol, which is expressed in micrograms per liter (μg/L).

Cases where heroin is judged to have been the source of the last antemortem administration of natural opioid.

Diazepam exposure in this context means the presence of diazepam or one of the approximately equipotent drugs which forms during its metabolism (desmethyldiazepam, oxazepam or temazepam). The drug concentrations are for diazepam itself.

Comparative concentrations of drugs in methadone, buprenorphine, and implant naltrexone treatment groups

The same drug families were present in patients from all the treatment groups, in similar mixtures and with similar representations (Table 1). The rates of opioid exposure were comparably high in all three groups, but morphine itself was more commonly detected in the naltrexone treatment group (Table 2). The concentrations of total morphine and free morphine, however, did not differ significantly between the treatment groups. Benzodiazepines were the second most commonly detected drug class, detected in 112 cases (76.2% of all drug/alcohol-related deaths). Diazepam and/or a metabolite (desmethyldiazepam, temazepam, oxazepam) were present in 104 of the 112 benzodiazepine-positive cases and diazepam itself was measurable in 70 cases. Oxazepam and temazepam are marketed drugs, as well as being diazepam metabolites, offering an alternate explanation for their detection in some cases. Alprazolam was present in 22 cases and other benzodiazepine in further 13 cases (Table 2). Neither the blood concentrations of diazepam nor the concentrations of any of its metabolites differed significantly between the three treatment groups (Table 2).

Alcohol was detected in 38 cases. The average blood alcohol concentration was 0.130 ± 0.141% in these cases (median 0.101%, IQR 0.051–0.177%). Alcohol was detected in significantly fewer of the naltrexone group patients, as observed previously (17). However, the concentrations did not differ significantly between the groups.

Antidepressants were present in 55 cases (37.2%). Antidepressant concentrations in most cases were consistent with conventional therapeutic use. Antipsychotic drugs were present in 34 cases, most commonly quetiapine (17 cases). The concentrations of antidepressant drugs and antipsychotic drugs did not differ significantly in inter-group comparisons. Phenylethylamine (amphetamine family) stimulants or cocaine metabolites were present in 36 cases (24.3%). Amphetamines and methamphetamines were both detected in 29 of these (19.7%). The treatments groups did not differ in the proportions involving any of these drug groups and nor were there significant differences in individual drug concentrations between the three
treatment groups. Tetrahydrocannabinol and carboxy-
tetrahydrocannabinol were detected in 35 cases with
carboxy-tetrahydrocannabinol alone detected in
a further four (26.4% in total). There were no signifi-
cant differences in the incidences or concentrations
between the treatment groups. The tetrahydrocannabi-
non concentration did not exceed 10 μg/L in any case.

Effects of addiction treatments and phase of
treatment on toxicological profile

Toxicological profiles in treatment groups
Thirty-eight patients died while on treatment (2.3 ptpy)
and 109 died off treatment (4.4 ptpy). While
a significantly higher percentage of patients off-
treatment had exposure to morphine (both free and
total) or heroin, the blood concentrations of these
drugs were not significantly different in patients dying
on treatment and off treatment (Table 3). Methadone
was more likely to be present in cases dying on treat-
ment than off treatment, but again the actual concentra-
tions of methadone in on-treatment and off-treatment
deaths were similar.

Drug exposures were then compared for 38 patients
who died while on treatment. As expected, methadone
was detected more commonly in patients from the
methadone treatment group and buprenorphine was
detected more commonly in patients from the bupre-
norphine-treated group. There were no other signifi-
cant differences in the proportions or levels of alcohol,
other opioids, benzodiazepines, stimulants or other
intoxicants between members of the three groups
dying on treatment. Nor were there any significant
differences in the blood concentrations of drugs
between patients in the three treatment groups dying
on treatment. Methadone was present in postmortem
analyses from 15 patients who were not enrolled in
a methadone program at the time of death.

Among the 109 patients dying off treatment, the
proportion of deaths involving alcohol was significantly
lower in naltrexone-treated patients compared with
methadone treated patients (OR: 0.13, CI: 0.03–0.61,
\( p = .010 \)), as we had previously observed (17). The
levels of alcohol, however, did not differ significantly
between the decedents from the three off-treatment
groups. There were no other significant difference in
the incidences or blood levels of intoxicants between
the three off-treatment groups. Unprescribed metha-
done was detected in 12.8% of all off-treatment deaths
(14 cases: Table 3), at comparable incidence in the
pharmacotherapy groups. Buprenorphine was not
detected in any patient dying off treatment. Drug com-
bined combinations followed similar patterns and incidences
in the on-treatment and off-treatment groups (Table 4).

Methadone induction
The first month of methadone treatment has been recog-
nized as a time of special vulnerability to drug-related
death (17). To explore this vulnerability further, we
compared methadone doses, blood levels and co-
toxicants in patients dying during methadone induc-
ion and later. Deaths within the induction period (first
28 days of treatment) predominately occurred around the
end of the first week (median: 7.5, IQR: 5.25–9.25 days),
at a time when the average treatment dose was 38.1 mg
day (median: 35.0, IQR: 30.0–40.0 mg). Beyond the

Table 3. On- and off-treatment blood levels (median and range) and drug detection rates in patients treated with methadone,
buprenorphine, and implant naltrexone, who died of alcohol or other drug poisoning.

<table>
<thead>
<tr>
<th>Drug Detection Rate (percentage &amp; number)</th>
<th>Blood Concentration (median &amp; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Detection Rate (percentage &amp; number)</td>
<td>Blood Concentration (median &amp; range)</td>
</tr>
<tr>
<td>On treatment</td>
<td>Off treatment</td>
</tr>
<tr>
<td>Any opioid</td>
<td>84.2% (32)</td>
</tr>
<tr>
<td>Morphine (total)</td>
<td>28.9% (11)</td>
</tr>
<tr>
<td>Morphine (free)</td>
<td>26.3% (10)</td>
</tr>
<tr>
<td>Heroin</td>
<td>21.1% (8)</td>
</tr>
<tr>
<td>Methadone</td>
<td>60.5% (23)b</td>
</tr>
<tr>
<td>Oxycodeone, buprenorphine or fentanyl</td>
<td>15.8% (6)</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>0.5% (0.03–0.86)</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>26.3% (10)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>81.6% (31)</td>
</tr>
<tr>
<td>Other benzodiazepines</td>
<td>10.5% (4)</td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>23.7% (9)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>15.8% (6)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>18.4% (7)</td>
</tr>
</tbody>
</table>

aDrug concentrations in blood, so excluding the four patients where only liver was available for analysis, all of whom died off treatment. Drug concentrations
are expressed in milligrams per liter (mg/L), except alcohol, which is expressed in grams per deciliter (%) and tetrahydrocannabinol, which is expressed in
micrograms per liter (μg/L).

b22 patients on prescribed methadone.

cOpioids of intermediate or low systemic potency (propoxyphene, tramadol, dextromethorphan, pholcodine) are not included in the table. Potent opioids that
appeared at very low incidence, such as pethidine (meperidine) are also not individually listed.

dDetection rates are for diazepam or a metabolite, including desmethyldiazepam, oxazepam or temazepam. Concentration data are for diazepam itself.

\( **p < 0.01 \), compared with on-treatment group; \( ***p < 0.001 \), compared with on- treatment group.
induction period, most deaths in the methadone treatment group occurred in patients who had been taking methadone for over 12 months (median: 759.5, IQR: 461–1181.75 days). Among these patients, the average daily dose of methadone in the month prior to death was 70.0 mg/day (median: 90, IQR: 27.5–100.0 mg). Patients in the methadone group who died after the first month included a majority who were taking stable maintenance doses (80–120 mg, n = 9) and a minority who appeared to be reducing their doses (<30 mg, n = 5).

As expected from their relative doses, patients who died during the induction period had significantly lower blood methadone concentrations (median: 0.25, range 0.06–0.80 mg/L) than those who died during the stable period (median: 0.70, range: 0.10–1.60 mg/L, p = .029).

Natural opioids (natural, underivatized products of the opium poppy, such as morphine and codeine), synthetic opioids, benzodiazepines, alcohol, tetrahydrocannabinol, and amphetamines were found at comparable rates and concentrations in patients dying during the induction phase and later. Benzodiazepine (predominantly diazepam and/or a metabolite) were very common in deaths occurring during induction (11/12) and on later treatment (11/14). Blood levels of diazepam, the commonest of the benzodiazepines in these patients, were not significantly different between those who died during induction (median: 0.2, range: 0.01–0.7 mg/L) and those who died later in treatment (median: 0.1, range: 0.07–0.4 mg/L). Diazepam metabolite levels were also comparable.

### Discussion

#### Alcohol and other drug involvement in deaths

As expected, opioids were the most common drugs detected in all treatment groups. Quantitative comparisons of specific opioids did not suggest differential susceptibility to opioid lethality between groups or phases of treatment. In agreement with previous studies, the majority of opioid overdose deaths occurred through combination with alcohol and/or benzodiazepines (26,27). Levels of benzodiazepines were within the broad range encountered during therapeutic prescribing. Although postmortem redistribution precludes a strict comparison between therapeutic and postmortem blood levels, this observation re-emphasizing the fact that even therapeutic amounts can acquire lethal potential in the presence of opioids.

An earlier inspection of these data had detected small, but significant differences between the groups in drug-specific mortality, raising a concern that patients in the three treatments did differ in their susceptibility to lethal toxicity and certain specific intoxicants (17). However, apart from the previously observed lower incidence of alcohol detection in patients who had been on the implant naltrexone program, we found no material differences between the three groups in the combinations or concentrations of other drugs. The concentrations of alcohol were comparable in the three groups. Naltrexone does help to restrain drinking (28), but most deaths in the naltrexone group occurred in treatment defaulters. The explanation is therefore tenuous.

Nine deaths occurred in patients in buprenorphine programs. Buprenorphine’s potency means that it can still exert agonist activity at concentrations that challenge detection in postmortem blood. That impedes confident measurement of its contribution to lethality in these cases. Buprenorphine, as a partial agonist at the \( \mu \) opioid receptor, has more limited potential to suppress respiration (22). That improves safety in overdose, compared with full agonists, such as methadone (15,29,30). It is not clear whether this also translates into improved safety when maintenance doses of buprenorphine are combined with other opioids or respiratory depressant non-opioids (15,31).

### On- and off-treatment deaths and diversion of treatment drugs

The re-escalation of mortality after defaulting from a treatment program has been observed in these patient groups and many others. We found that the drugs that caused death off-treatment were largely the same as those causing on-treatment deaths. As expected, methadone was found more commonly in on-treatment deaths in the methadone group. The concentrations of methadone were not significantly different between those patients in a treatment program and those using non-prescribed methadone, except for the first month.
of treatment, as discussed further below. Morphine was identified in a significantly higher percentage of deaths off treatment, compared with on treatment. The blood concentrations of both free and total morphine were comparable in patients dying on and off treatment, though. Evidence for heroin use was commoner in the off-treatment patients, indicating that this difference is at least partially attributable to returning to the use of heroin. The percentages and concentrations of other drugs, including benzodiazepines, were not significantly different between patients who died on or off treatment. Similarly, the combinations of drug types involved in the fatalities on and off treatment did not differ.

Diversion of prescribed methadone or buprenorphine complicates comparisons between treatment groups and phases of treatment. Unprescribed methadone appeared in postmortem blood in 15 cases. Buprenorphine was not detected in patients dying off treatment. However, the absence of buprenorphine does not confirm that there was no diversion or that diverted buprenorphine was not involved in any of the off-treatment deaths.

**Methadone induction**

The first month, and particularly around the end of the first week of treatment, was confirmed as a time of particular vulnerability to drug overdose death in new recruits to methadone programs. The toxicological profiles of methadone patients did not differ significantly between the first month on treatment and the subsequent treatment period, with the exception of the blood methadone concentration itself. The methadone dose and the measured postmortem methadone concentration were lower in deaths occurring during induction than in methadone maintenance patients dying later, as expected during a dose-titration phase. The relative contribution of methadone itself to death in these patients cannot be confidently assessed because methadone concentrations in patients dying of drug overdose overlap substantially with methadone maintenance patients dying of incidental causes (32). Although adherence to a methadone program improves survival in opioid dependency, it is an opioid drug and our data affirm it as a contributor to death in methadone maintenance patients who resume opioid use or take other sedating drugs.

**Limitations**

The study was a retrospective examination of treatment and treatment outcomes. The patients appeared equivalent in demographic information but were not allocated randomly to the three treatment programs. Consequently, there may be underlying differences between the groups. Similarly, we did not have information on the pre-treatment opioid and other drugs use, which may have contributed to their post-treatment deaths. The study also employed health data sets that were complete for events that occurred within the state, but may not have captured events occurring outside the state. That might include out-of-state deaths.

The data may also underestimate the importance of buprenorphine and naltrexone, because they are effective at low concentrations that may not have been routinely detected using the blood screening methodologies employed early during the study period. Patterns of drug choice also change over time, with novel agents appearing and disappearing. These data were collected before high potency novel opioids, like sufentanil and carfentanil, and potent novel benzodiazepines became available in the study community. Synthetic cannabinoid use was also still at a very low level and the use of novel stimulants (phenethylamine and other) was not prevalent. Undoubtedly, these drugs have lethal potential that equals or exceeds the lethal potential of older drugs. They would therefore be anticipated contributors to some deaths occurring in the years after our study data were collected. However, there is no a-priori reason to expect that patients on different treatments for opioid dependency would be materially different from one another in their vulnerability to these new members of the opioids, benzodiazepine, stimulant, and cannabinoid drug families.

**Conclusions**

In conclusion, 41,188 patient-years of follow up of patients in methadone, buprenorphine, and implant naltrexone programs showed that drug-related deaths in the three treatment groups were caused by similar patterns of drug exposure. Most deaths were caused by drug mixtures, with opioids and benzodiazepine co-intoxication the commonest cause in all treatment groups and all phases of treatment. Moving off treatment increased the likelihood that heroin contributed to death. Concentrations of drugs were mostly comparable between the treatment groups and between on-treatment and off-treatment phases. That is not surprising, given that a patient’s capacity to survive a particular drug concentration is an ill-defined function of intoxicant doses, tolerance, and protection by therapy. However, it does argue that previously observed differences between treatment groups in
drug-specific mortality are not clinically important. The first month of methadone treatment, and particularly around the end of the first week, was confirmed as a time of increased vulnerability.

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