OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Original Research Article

Post-marketing Surveillance of Methadone and Buprenorphine in the United States

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Abstract

Introduction. There have been recent increases in the use of methadone and buprenorphine in the United States. Methadone is increasingly being used for pain management, and buprenorphine use has expanded to include treatment for opioid addiction, leading to exposures of these drugs in new populations. There is a debate about the relative safety of these two drugs in routine outpatient medical use.

Methods. Data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Programs were used to analyze rates of abuse, misuse, and diversion using the Drug Diversion, Key Informant, Poison Center and Opioid Treatment Programs, 2003–2007. National rate and rate ratios were calculated using population and person-time exposed denominators. Detailed data are presented on severity of medical outcome and drug formulations.

Results. Between 2003 and 2007, there were steady increases in the rates of abuse, misuse, and diversion of both methadone and buprenorphine. Rate ratios (per 100,000 population per quarter) of abuse, misuse, and diversion were consistently higher for methadone than buprenorphine. RADARS System poison centers received 7,476 calls for methadone and 1,117 calls for buprenorphine. After accounting for availability, there were higher rates of calls for methadone misuse, abuse, and diversion than buprenorphine in three of the four programs. The numbers of exposures requiring medical attention correspond to 46.8% and 25.8% of all calls, for methadone and buprenorphine, respectively. The most commonly diverted form of methadone was solid oral tablets (which are typically dispensed at pharmacies, not at opioid treatment programs), comprising 73% of cases.

Conclusions. Buprenorphine appears to have a better safety profile than methadone during routine outpatient medical use. However, both medications have roles in the treatment of pain and opioid addiction, and further research into their respective benefits and risks should be conducted.
Relative Safety of Methadone and Buprenorphine

In the United States, there were substantial increases in opioid prescriptions in the outpatient setting during the 2000s for both methadone and buprenorphine, and other opioid analgesics [21–25]. Prior to 2003, buprenorphine was primarily used for pain management in the United States; since October, 2002, buprenorphine has been approved for the management of opioid dependence, and therefore entered a different patient population than had previously been prescribed buprenorphine (i.e., for pain). The medical uses of the only previously FDA approved buprenorphine product (Buprenex®) were predominantly in the hospitals or clinics for analgesia, with occasional off-label use for short-term opioid withdrawal; the liquid injectable formulation may have limited its use in outpatient therapy. On the other hand, the sublingual formulations Suboxone® (buprenorphine HCl/naloxone HCl) and Subutex® (buprenorphine HCl) are primarily intended for outpatient use, when prescribed for the treatment of opioid dependence. Clinicians are required to undergo a condensed training program in order to be able to prescribe the sublingual formulations for management of opioid dependence. With methadone, there was a shift in the opposite direction, with increased use in outpatient pain management [21,26], while the previous experience in the United States had been in patients with opioid dependence. Methadone maintenance programs are tightly regulated, with requirements on starting doses, titration, observed daily dosing, and a very limited range of options for take home doses. The formulation of methadone used in outpatient pain management (solid oral tablets) is generally different from those used for maintenance pharmacotherapy for opioid dependence (DISKETS® Dispersible Tablets). In summary, in the early 2000s medical use of buprenorphine and methadone in the United States present a natural experiment; there were opposite shifts in patient population with simultaneous expanded outpatient use of both medications.

Despite the fact that both buprenorphine and methadone are effective for the management of opioid addiction [27,28], there is debate about which medication is safer for outpatient use. The World Health Organization’s Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence state: “Overall, while buprenorphine itself is likely to be a safer medication, the difficulty of quantifying these benefits and comparing them with the risks of diversion and injection of buprenorphine mean that no conclusions on safety differences can be drawn.” (pp. 30–31). Evidence from France suggests that large-scale, free access to buprenorphine accompanied by harm reduction measures can have dramatic effects on overdose mortality, crime, incidence of human immuno-deficiency virus (HIV) infection, and injection drug use [29–31], with relatively low mortality from buprenorphine compared with methadone when accounting for the medical use [31]. Evidence from Europe and Australia suggests that buprenorphine may have a safer profile than methadone during induction periods at the beginning of

Key Words. Methadone; Buprenorphine; Opioid; Post-Marketing; Surveillance; Safety; Diversion; Poisoning

Introduction

Methadone and sublingual buprenorphine are both used to treat opioid dependence in the United States. Methadone, but not sublingual buprenorphine, is also approved by the Food and Drug Administration (FDA) to treat pain. Controversy has developed regarding the abuse of these drugs and their potentially lethal effects when not used as directed. Mortality from methadone poisonings has driven part of the debate about the role of this opioid in outpatient medical care. The number of methadone poisoning-related deaths as reported on death certificates increased from 754 in 1999 to 2361 in 2002, a 213% change [1]; these deaths are from methadone used for pain as well as addiction, with state-level studies suggesting that relatively few deaths are from methadone prescribed for addiction treatment [2]. The number of buprenorphine poisoning-related deaths in the United States is currently unknown.

Both buprenorphine and methadone have the potential to be used nonmedically based on pharmacological investigations [3,4]. A study conducted in 2005 at methadone treatment centers found that 8.2% of enrollees endorsed methadone as the primary drug “used to get high” in the 30 days prior to admission, while 0.1% of these enrollees endorsed buprenorphine as the primary drug of abuse [5]. Methadone is diverted as evidenced by data from drug diversion authorities [6], and the Drug Enforcement Agency (DEA); diversion and street prices of buprenorphine were used to justify rescheduling [7]. Both DEA and FDA have expressed concerns about methadone diversion and poisoning [8], resulting in the “voluntary agreement” in December 2007 by manufacturers to restrict distribution of the 40-mg dispersible dosage form for pain, with it only being available to methadone maintenance and detoxification programs [9]. The increased use of methadone in pain management has paralleled increases in the medical consequences associated with overdose in many observational studies in the United States [10–15], which also holds true for other opioid pain relievers, although likely to a lesser extent [10,16]. Concerns about QT prolongation and torsades de pointes (TdP) ventricular arrhythmia also exist for methadone [17,18].

The clinical experience with buprenorphine for addiction treatment in the United States has only occurred since the passage of the Drug Abuse Treatment Act of 2000. Data on buprenorphine were not reported in standard National Survey on Drug Use and Health reports because of the low numbers of respondents endorsing nonmedical use in the year preceding interview, but a study sponsored by the Substance Abuse and Mental Health Services Administration concluded that abuse of buprenorphine was low relative to hydrocodone and oxycodone [19]. The number of patients receiving buprenorphine for addiction treatment increased more than sixfold from 2005 to 2007, with nearly 300,000 individuals treated in 2007 [20].

Relative Safety of Methadone and Buprenorphine

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oral substitution therapy, and there is continuing research as to the relative safety of the two medicines [32–39]. Mortality from toxic buprenorphine exposure is most commonly observed when the drug is abused in conjunction with benzodiazepines [31,40–45]. Despite information from other countries, little has been published on the relative experiences with buprenorphine and methadone in the United States during the 2000s, particularly related to diversion. To provide perspective on the debate of the relative safety of buprenorphine and methadone, in this paper, we present data on post-marketing surveillance for these two opioids. In this study, we reviewed cases of abuse, misuse, and diversion (see below for definitions) of methadone and buprenorphine in the United States between 2003 and 2007.

Methods

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System is national surveillance system that monitors the abuse, misuse, and diversion of prescription opioids [46]. In this paper, we use data from four component programs of the RADARS System: Drug Diversion, Key Informant, Poison Center and Opioid Treatment Programs.

RADARS System Programs

RADARS System data offer multiple perspectives on prescription drug abuse through the use of seven unique programs that collect and report data on a quarterly basis, with geographic specificity (three-digit ZIP code level) throughout the United States. Each program captures unique data; they are designed to capture data from different target populations, representing different stages in the natural histories of substance use disorders, such as interaction with law enforcement, entering drug treatment, acute poisoning events, etc. Collectively, these programs address the geographic component of prescription opioid abuse, misuse, and diversion and report data on non-abuser victims. Because three of these programs are relatively new and have limited historical data available, the four most developed programs in 2007 were selected for this analysis in order to be able to analyze time trends.

Drug Diversion Program

This RADARS System Program was composed of 302 prescription drug diversion investigators or regulatory agencies in 2007 who were surveyed quarterly and asked to report the number of new diversion cases investigated in that quarter. Cases were defined as the number of new instances of pharmaceutical diversion reported to or investigated by the diversion unit or regulatory board during the previous quarter. These must be official cases initiated during the previous quarter. As such, only cases in which there is a new written complaint or report were included. Cases were assigned to the three-digit ZIP code where the case occurred or, when the three-digit ZIP code where the case occurred is unknown, were redistributed across the informant’s jurisdiction. More detailed descriptions of the Drug Diversion Program have been published elsewhere [6,46,47].

Key Informant Program

In 2007, this RADARS System Program was composed of 217 key informants, leading professionals in the field of drug abuse such as clinicians, epidemiologists, treatment counselors, and others who are in positions to recognize and report on drug problems. Informants were surveyed quarterly and asked to report the number of new abuse cases known to the informant in that quarter. Cases were defined as use to get high, use in combination with other drugs to get high, or use as a substitute for other drugs of abuse as reported by health care professionals. Cases were assigned to the three-digit ZIP code of the key informant participating in the program. More detailed descriptions of the Key Informant Program have been published elsewhere [48–50].

Poison Center Program

In 2007, this RADARS System Program was composed of 43 of the 60 US Poison Centers. Participating poison centers sent cases for the RADARS System drugs of interest on a weekly basis to a central database maintained by the RADARS System. Each case was subject to a rigorous quality control process to verify the identity of the drugs involved and ensure coding accuracy. Cases were defined as any human intentional exposure call managed by participating poison centers involving methadone and/or buprenorphine. Intentional exposures are used as surrogates for abuse and misuse and are composed of the following categories which have standardized definitions within the poison center data collection system [51]: suicide, intentional misuse, abuse, intentional unknown, and withdrawal cases. Calls received to poison centers are handled and data entered by nurses and pharmacists who have training in clinical toxicology and passed a national certification exam [52]. Cases were assigned to the reported three-digit ZIP code of the exposed individual’s residence. More detailed descriptions of the Poison Center Program have been published elsewhere [53–55].

Opioid Treatment Program

This RADARS System Program was composed of 75 participating methadone treatment programs in 2007, representing a convenience sample with oversampling in rural areas and parts of the nation with known prescription opioid abuse problems. Patients enrolling at these treatment centers were asked to complete an anonymous questionnaire, which includes questions concerning the patients’ drug use in the past month, lifetime drug abuse, age at first use, and the primary source of the abused drugs. Cases were defined as self-reported use of a prescription or illicit opioid to get high in the past 30 days. Cases were assigned to the reported three-digit ZIP code
especially because these differences are poorly character-
gizes potency between methadone and buprenorphine,
of kilograms of opioid because of the difference in anal-
identifier to identify individuals across different pharmacies
name-based system by SDI, which generates a unique
ations received during that time. Multiple prescriptions
as a single URDD, regardless of the number of prescrip-
filling a prescription for a drug in a given quarter is counted
person-based measure (“denominator”); every individual
name-based identification algorithm. The URDD is a
mation. Duplicate prescriptions, refills within a given time
given time and place, based on pharmacy payment infor-
misuse” was defined as any use of the medication not as directed by the pre-
scription, but to address a medical need; for example, this
includes taking the opioid more often or in greater quan-
tities than as directed because of inadequate pain relief.
“Abuse” of the medication is intended to mean any use of
the opioid with the intent to achieve a psychotropic effect
(i.e., “get high”), outside of any supervised or directed
medical need. “Abuse” does not refer to a clinical diagno-
sis such as is used by the Diagnostic and Statistical
Manual, and subsumes both abuse and dependence con-
structs. “Diversion” signifies the willful illegal removal of a
controlled substance from the distribution chain or storage
of the patient for whom it was prescribed, for the purpose
distribution or sale, including acts by the patient.

Case Selection

The RADARS System Programs collect data on multiple
prescription opioids sold in the United States [46]. For the
purposes of this analysis, all cases involving buprenor-
phine and methadone through the end of 2007 were
selected from each component program, starting in 2003
for the Drug Diversion, Key Informant, and Poison Center
Programs, and starting at its inception in 2005 for Opioid
Treatment Program.

Calculation of Rates

Rates are calculated per 100,000 persons and per 1,000
unique recipients of a dispensed drug (URDD). Population
and URDD of the 3-digit ZIP code reporting into each
program was totaled based on the 2000 US Census and
reports from SDI (Plymouth Meeting, PA), respectively.
Rates per 100,000 persons provide a measure of the
overall public health significance. The use of URDDs to
calculate rates has been described elsewhere [56]. Briefly,
URDDs are a person–time denominator representing a
proprietary estimate of the number of unique individuals
being dispensed a prescription for the medication, in a
given time and place, based on pharmacy payment infor-
mation. Duplicate prescriptions, refills within a given time
unit, and other redundancies are accounted for through a
name-based identification algorithm. The URDD is a
person-based measure (“denominator”); every individual
filling a prescription for a drug in a given quarter is counted
as a single URDD, regardless of the number of prescrip-
tions received during that time. Multiple prescriptions
during each time period are tracked using a probabilistic
name-based system by SDI, which generates a unique
identifier to identify individuals across different pharmacies
and over multiple prescriptions. URDDs are used instead
of kilograms of opioid because of the difference in anal-
gesic potency between methadone and buprenorphine,
especially because these differences are poorly character-
ized by route of administration. URDDs are also used
instead of the number of prescriptions dispensed since
the drugs are in different Schedules as dictated by the
Controlled Substances Act and therefore subject to differ-
ent rules regarding refills and length of prescriptions
that may be written, in addition to being subject to specific law
and regulations pertaining to their use in the management
of opioid dependence in the United States [57–59]. URDD
is a reasonable proxy for the medical availability of an
opioid analgesic within a community, and rates per 1,000
URDD provide an indirect measure of exposure based on
a product’s medical availability [56]. Rate ratios are pre-
sent, which are ratios of the URDD rate for methadone
divided by the URDD rate for buprenorphine.

Statistical Analyses

Quarterly rates and relative rates for buprenorphine and
methadone, using URDD and population, for selected
RADARS System Programs were estimated using Poisson
regression, with generalized estimating equations (GEE)
for repeated measures in each three-digit ZIP code over
time, with a separate model for each program. GEE
models are commonly used in situations were repeated
observations of the same individual or community are
observed over time to account for the violation of the
assumption of the independence of each observation in
linear regression. Analyses were conducted in Statistical
Analysis Software v9.0 (Cary, NC).

Human Subjects

The protocols for data collection and analysis in the
RADARS System have been reviewed by the institutional
review boards at the Denver Health and Hospital Authority,
the Washington University of Saint Louis, the University
of Delaware, and the National Development and Research
Institutes, Inc. In addition, all participating poison centers
obtained institutional review board approval to participate
in the RADARS System.

Results

Between 2003 and 2007, there were steady increases in
the rates of abuse, misuse, and diversion of both metha-
done and buprenorphine, as reported to the RADARS
System. As seen in Figure 1, rates per 100,000 total
population per quarter increased in all four programs
during the study period. The rates of increase over time
are similar for both methadone and buprenorphine in three
of the four programs (Drug Diversion, Key Informant, and
Poison Center). The relative rates (per 100,000 population per quarter) of
abuse, misuse, and diversion were consistently higher for
methadone than for buprenorphine in all of the programs
(Table 1). Opioid Treatment Program had the highest rate
ratios (RR) of methadone abuse/misuse (RR: 15.3; 95%
confidence interval [CI]: 12.6, 18.5). New cases of metha-
done diversion as reported by law enforcement officials in
the RADARS System Drug Diversion Program were
second highest (RR: 10.1; 95% CI: 8.2, 12.3), followed by Poison Centers (RR: 6.3; 95% CI: 5.5, 7.1), and Key Informant (RR: 2.9; 95% CI: 2.3, 3.8). The precision of the estimates were similar across programs, but greatest for Poison Center (confidence limit ratio [CLR]: 1.28) and lowest for Key Informant (CLR: 1.65).

The number of URDDs was used to account for the differences in the amount of medical use of buprenorphine and methadone in rate calculations. URDDs are a person-based proxy for population level exposure to the two medicines. Relative to buprenorphine, rates per 1,000 URDD per quarter showed methadone to have a poorer safety profile in three programs: Drug Diversion (RR: 1.8; 95% CI: 1.4, 2.2), Poison Center (RR: 1.5; 95% CI: 1.3, 1.6), and Opioid Treatment (RR: 4.7; 95% CI: 3.8, 5.7). In the Key Informant Program, rates per 1,000 URDD per quarter showed methadone to have a better safety profile relative to buprenorphine (RR: 0.6; 95% CI: 0.5, 0.8) (Table 1). After initial instability in rates because of relatively small number of patients receiving buprenorphine in 2003 and 2004, the relative rates of methadone and buprenorphine abuse, misuse, and diversion have remained steady since 2005 for the Drug Diversion Program, and since 2006 for the Poison Center Program (Figure 2). Buprenorphine and methadone rates in the Key Informant Program converged by 2007, with similar rates of abuse being reported.

For some programs, it is possible to obtain more information on the nature of the cases which contributed to the rate. We present RADARS System Poison Center Program data for the associated medical outcomes for methadone and buprenorphine during the study period (Figure 3). During the study period, RADARS System poison centers received 7,476 calls for methadone and 1,117 calls for buprenorphine. For methadone, 3,500 calls were associated with major life-threatening events or
events requiring medical attention (moderate effects), vs 288 calls for buprenorphine. The numbers of exposures requiring medical attention correspond to 46.8% and 25.8% of all calls for each opioid received during the study period, for methadone and buprenorphine, respectively.

Further supporting the more severe medical consequences of methadone exposure, 140 deaths associated with methadone intentional exposures were reported to RADARS System Poison Centers, between 2003 and 2007, and five for buprenorphine. However, a causal connection is not made between the presence of the opioid and death in poison center data.

To further explore the relative contribution of opioids from the two different indications (i.e., pain and addiction), we examined the formulation type giving rise to cases in RADARS System Programs during the study period, see Table 2. The most striking finding is that 73% of methadone cases reported in Drug Diversion were tablets, the formulation used for outpatient pain management. This is also mirrored in the Poison Center data, but the large proportion of unspecified methadone dosage forms prevents us from drawing firm conclusions. However, the dosage form for buprenorphine is much better specified in Poison Center data.

Discussion

This analysis of RADARS System data confirms that there was an increase in the unintended consequences associated with outpatient use of both methadone and buprenorphine between 2003 and 2007. Patients entering opioid treatment programs reported the highest rates of methadone use to get high in the first half of 2006, with rates decreasing after that time. National mortality data from 2007 are not yet available for comparison, but hospital emergency department (ED) mentions reported to the Drug Abuse Warning Network increased from 42,491 ED visits (CI: 31,831 to 53,151) in 2004 to 45,130 ED visits (CI: 35,870 to 54,389) in 2006 [60,61]. It remains to be seen if there will be subsequent decreases in ED visits corresponding to the data observed in the RADARS System Opioid Treatment Program.

When calculated using the total population denominator, rates of abuse, misuse, and diversion of methadone far exceeded that of buprenorphine on average in all but one of the RADARS System Programs examined in this analysis. These results suggest a greater overall public health and law enforcement burden associated with methadone, relative to buprenorphine. Accounting for a proxy of drug exposure (availability using the URDD denominator), methadone still exceeded buprenorphine in three of the RADARS System Programs, although the margin of difference was less.

One of the important findings of our analysis is the severity of the outcomes associated with buprenorphine and methadone among poison center calls. Buprenorphine was consistently associated with less severe acute consequences after exposure compared with methadone. While there are pharmacologic rationales for this observation, we present here the first analysis comparing these two drugs in routine medical practice that links individual exposures to medical outcomes in the United States. As others have noted, poison center data must be analyzed with care, and with particular attention paid to the strengths and weaknesses of the data source [52]. In this instance, poison centers’ data collection structure allowed us to provide a more in-depth comparison between the two drugs of interest.

### Table 1  Rate ratios of reports of abuse, misuse, and diversion associated with prescription opioids, per quarter, by Program, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System reporters, United States, 2003–07

<table>
<thead>
<tr>
<th>RADARS System Program</th>
<th>Drug Diversion</th>
<th>Key Informant</th>
<th>Poison Center</th>
<th>Opioid Treatment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Rate Ratio, per 100,000 population, per quarter</td>
<td></td>
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</tr>
<tr>
<td>Buprenorphine</td>
<td>1.</td>
<td>1.</td>
<td></td>
<td>1.</td>
</tr>
<tr>
<td>Methadone</td>
<td>10.06 (8.21, 12.33)</td>
<td>2.94 (2.29, 3.78)</td>
<td>6.26 (5.54, 7.07)</td>
<td>15.26 (12.58, 18.51)</td>
</tr>
<tr>
<td>CLR = 1.50</td>
<td>CLR = 1.65</td>
<td>CLR = 1.28</td>
<td>CLR = 1.47</td>
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<tr>
<td>Average Rate Ratio, per 1000 URDD‡, per quarter</td>
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<tr>
<td>Buprenorphine</td>
<td>1.</td>
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</tr>
<tr>
<td>Methadone</td>
<td>1.76 (1.41, 2.20)</td>
<td>0.64 (0.52, 0.80)</td>
<td>1.47 (1.34, 1.62)</td>
<td>4.69 (3.84, 5.74)</td>
</tr>
<tr>
<td>CLR = 1.56</td>
<td>CLR = 1.53</td>
<td>CLR = 1.21</td>
<td>CLR = 1.49</td>
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</tr>
</tbody>
</table>

† Data from Opioid Treatment Program are from 2005–2007.
‡ URDD = Unique Recipient of Dispensed Drug, number of unique individuals filling prescriptions in outpatient pharmacies per quarter, derived from commercial vendors.
CLR = confidence limit ratio.
The demand for diverted methadone, as reported by participants in the Opioid Treatment Program, may suggest an unmet treatment need, or attempts by opioid dependent individuals to try methadone for withdrawal management before enrolling in a program, in addition to endorsement for psychotropic effects of euphoria (to “get high”). Similar reasons for trying diverted methadone before entering drug treatment have been observed in studies of youth (25 year-olds and younger) in drug treatment, HIV positive drug users, and out of treatment urban “street users” [62–64]. Previous treatment experiences play a key role in determining whether patients receive methadone or buprenorphine [65], suggesting an explanation why rates of nonmedical use of buprenorphine and methadone are different between the Key Informant Program (many buprenorphine prescribers) compared

Figure 2 Rate of abuse, misuse, and diversion per 1,000 unique recipients of a dispensed drug (URDD) per quarter, two-period moving averages, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, 2003–2007, Unites States. Rates of abuse, misuse, and diversion in the RADARS System were calculated with a denominator intended to account for differences in outpatient medical use (i.e., availability) of methadone and buprenorphine using the respective number of unique individuals dispensed with the drug in a given quarter (URDD, see text for explanation). After accounting for availability, methadone had higher rates of abuse, misuse, and diversion in the three programs for most of the study period. While initially higher in the Key Informant Program, rates of buprenorphine and methadone abuse and misuse had converged by 2007. RADARS System Poison Centers showed steadily increasing calls involving abuse and misuse of buprenorphine during the first 2 years or marketing of Suboxone and Subutex, with constant stable rates starting in the fourth year. Methadone abuse and misuse in the Opioid Treatment Program peaked in early 2006. URDD-adjusted rates in the Drug Diversion Program were higher during the early phases of Suboxone and Subutex availability, but showed consistent rates after the first year and a half of marketing. Methadone formulations in this figure include both those used for pain and agonist therapy for the management of opioid dependence. Opioid Treatment Program data are presented from inception of data collection in 2005.
with the Opioid Treatment Program (mostly outpatient methadone clinics). Among the key informants, many of whom are buprenorphine prescribers, we may be observing a similar phenomenon as observed with those entering methadone maintenance programs, with some diverted buprenorphine being used for self-management of withdrawal before entering drug treatment. However, substantial proportions of participants in both programs also endorsed the use of the medications “to get high” in the month previous to interview. In a previous analysis of these Key Informant data, the authors concluded that the observed increase in nonmedical buprenorphine use was

Figure 3  Number of calls and associated medical outcomes for intentional exposures mentions for methadone and buprenorphine, Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center, 2003–07. Calls to RADARS System Poison Centers for methadone and buprenorphine showed different patterns of medical outcome severity for acute poisoning events. A greater proportion of methadone calls were associated with major life-threatening medical outcomes or death than buprenorphine calls. Standardized definitions of associated medical outcomes were used according to the American Association of Poison Control Centers National Poison Data System (see text), and recorded by trained toxicology specialists in poison information. Medical outcome refers to the disposition of the subject of a poison center call associated temporally with the drug exposure. The numbers at the top of each column are the absolute number of calls received, and the vertical axis represents the percentage of calls for each type of associated medical outcome, separately for methadone and buprenorphine. Calls not followed indicates situations where the poison center was not able to determine the disposition of the individual after follow-up with the caller, local hospitals and emergency medical services; some of these calls may have resulted in a serious life-threatening event.
because of experimentation by polysubstance users [66]. While key informants were routinely presented with the opportunity to specify the formulation, the high proportion (52.5%) of key informants who did not note which buprenorphine formulation was abused makes it difficult to draw firm conclusions from this program alone.

It is well established that exposure to opioid agonist therapy reduces long-term mortality among those with opioid dependence, for both methadone and buprenorphine [30,32,33,35–37,67–71], and evidence from the United States that arrests are also decreased with long-term substitution therapy [72]. Studies in other countries have suggested lower mortality rates for patients on buprenorphine compared with methadone for the management of opioid dependence [37,38], although observational studies suggest mortality strongly reflects national-level policy regarding to whom and how treatment is delivered, and the relative amounts of each drug dispensed [73]. Additionally, the relative safety of buprenorphine in accidental pediatric exposures (compared with full mu-opioid receptor agonist opioids) has been reported by RADARS System researchers [74] and others [75]. However, in the United States the considerable use of methadone for pain makes the comparison more difficult in a mixed age population.

Deaths associated with methadone were much more commonly reported to RADARS System Poison Centers than for buprenorphine; rates adjusting for availability showed similar results. Taken together with observations from other comparative studies, the relative safety of buprenorphine over methadone has credence.

Medical examiner and coronial records indicated the difficulty in ascertaining the causal effect of drug exposure on fatal poisoning by methadone or buprenorphine [43,76–78]. Poison center staff does not conduct as thorough a physical investigation as medical examiners do, and the counts of calls to RADARS System Poison Centers should not be interpreted as absolute numbers of deaths associated with these drugs. Because we are concerned primarily with the relative safety of buprenorphine over methadone has credence.

### Table 2

<table>
<thead>
<tr>
<th>Primary Medical Use</th>
<th>RADARS System Program</th>
<th>Drug Diversion</th>
<th>Key Informant</th>
<th>Poison Center</th>
<th>Opioid Treatment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subutex</td>
<td>opioid addiction</td>
<td>NA</td>
<td>4.8% (127)</td>
<td>7.9% (96)</td>
<td>NA</td>
</tr>
<tr>
<td>Suboxone</td>
<td>opioid addiction</td>
<td>40.6% (1072)</td>
<td>85.0% (1036)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenex</td>
<td>acute pain</td>
<td>2.1% (55)</td>
<td>1.5% (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td></td>
<td>52.5% (1386)</td>
<td>5.5% (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100% (2640)</td>
<td>100% (1218)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid</td>
<td>opioid addiction</td>
<td>15.6% (513)</td>
<td>5.1% (424)§</td>
<td>21.7% (1793)</td>
<td></td>
</tr>
<tr>
<td>Wafer/diskette</td>
<td>addiction &amp; pain‡</td>
<td>(0)</td>
<td>(0)</td>
<td>38.5% (3191)</td>
<td></td>
</tr>
<tr>
<td>Tablet</td>
<td>chronic pain</td>
<td>72.9% (2391)</td>
<td>25.9% (2155)</td>
<td>39.8% (3292)</td>
<td></td>
</tr>
<tr>
<td>Not specified &amp; other††</td>
<td></td>
<td>11.4% (375)</td>
<td>69.0% (5751)‖‡</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100% (3279)</td>
<td>100% (8330)‖§</td>
<td>100% (8276)</td>
<td></td>
</tr>
</tbody>
</table>

† Data from Opioid Treatment Program are from 2005–2007.
‡ Includes Subutex reported in combination with Suboxone (1 call) and Buprenex (1 call).
§ Includes two mentions of injectable methadone.
‖ As of December 2007 the 40 mg diskettes could no longer be purchased in outpatient pharmacies, and were limited to distribution only via methadone maintenance programs.
‖‖ For Drug Diversion numbers in this table, “other” category includes seizures of wafer/diskette, crushed tablets, powder and patches.
‡‡ Includes four mentions of powder methadone.
§§ There were 314 calls in which both liquid and tablet methadone were ingested.
both substances. To address this, poison center call notes were reviewed by the RADARS System to update codes for the substances involved if there were follow-up clinical notes of a differential diagnosis. However, spontaneous reports such as these cannot be used to systematically determine causality for single substances in instances of polypharmacy.

The overwhelming majority (85%) of Poison Center calls involving buprenorphine were for the buprenorphine formulation containing naloxone, Suboxone, reflecting its relative market share to Subutex in the United States during the study period [20]. We cannot conclude from these data whether the observed relative safety of buprenorphine compared with methadone (as evidenced by less severe acute medical events) is a function of buprenorphine or of its combination with naloxone. Pharmacologic studies suggest that the safety aspect (reduced risk for respiratory depression) is driven by the buprenorphine component of Suboxone and not naloxone [3,79], although this is an area of active research and debate [29,30,80,81].

In order to account for the increased outpatient medical use of methadone and buprenorphine, we calculated rates using a person-time denominator that serves as a proxy for human outpatient exposure time and drug availability, the URDD. However, using URDDs also has limitations. Patients receiving methadone in maintenance treatment programs are not recorded by commercial vendors who primarily draw their data from reimbursement-oriented switches in pharmacy computer systems. However, because only a small portion of methadone maintenance treatment program patients regularly receive more than a weekend’s worth of methadone for take home, including all methadone maintenance treatment program patients would artificially increase the denominator for rate calculations. State-level data from the United States [2,13] and Germany [82] suggest that most methadone-associated deaths do not occur among patients in methadone maintenance, even though there are well-documented risk periods during induction when there is an elevated risk of death from respiratory depression. To address the concern of not accounting for take home methadone doses in the URDD denominator, we searched for information on the number of methadone maintenance patients receiving take home doses, but these figures were not available. The only public estimate of the number of methadone maintenance treatment program patients comes from the National Survey of Substance Abuse Treatment Services (N-SSATS), an annual single-day cross-sectional survey of the number of patients in methadone maintenance treatment programs; program response is voluntary and is not tied to incentives. On March 31, 2006 (the latest year for which data are available), there were 257,919 patients enrolled in the 1203 opioid treatment programs that responded to the N-SSATS questionnaire (response proportion: 0.965). This is compared with 410,118 patients receiving methadone in outpatient pharmacies, presumably (and according to law) for pain management, in the first quarter of 2006 (SDI, Plymouth Meeting, PA). Based on sensitivity analyses under different conditions of the proportion of take home doses, we found our findings to be robust even under theoretical conditions where 30–40% of methadone maintenance patients received take home doses, albeit with reductions in precision. For the sake of brevity, the details of this sensitivity analysis are not presented in this paper. However, the inability to precisely account for take home methadone doses is a broader data collection problem in the United States.

There are considerable state-level variations in the number of methadone maintenance providers and clinicians who are waivered to prescribe buprenorphine for addiction, as evidenced by the Substance Abuse and Mental Health Services Administration’s (SAMHSA) Substance Abuse Treatment Facility Locator (http://findtreatment.samhsa.gov/) and Medicaid structures [83]. Similarly, state-level variations in methadone use may exist, based partially on pharmacy benefit managers requiring the use of methadone as the first-line therapy for moderate to severe chronic pain which requires around the clock analgesia, a cheaper proposition than using most branded extended-release opioids. There is also considerable variation between treatment settings for methadone maintenance treatment and doctors’ office-based buprenorphine; assuming a degree of patient knowledge, access and agency in choice, may predispose certain patients to seek the treatment modality better suited for them. Finally, the medical specialties involved in pain and addiction medicine are different, and there are differences in training educational requirements to prescribe methadone (none) vs buprenorphine (training course, registration) to treat for addiction. These factors may also play a role in the differences we observed between the relative safety of buprenorphine and methadone in post-marketing surveillance.

Formulations of both buprenorphine and methadone have legitimate medical uses in the treatment of pain and opioid addiction. The debate about the relative safety of these two medications requires further research into abuse, misuse, and diversion during routine medical use. In this paper, we provide empirical support for using multiple perspectives to understand the relative safety profiles of these two medications, a methodology that can be extended to other controlled pharmaceutical medications and has been suggested by others [11].

Conclusions

The abuse, misuse, and diversion of both buprenorphine and methadone were increasing through 2007. While these post-marketing surveillance data suggest a better safety profile for buprenorphine compared with methadone, these data must be interpreted with caution. The use of methadone for outpatient management of chronic pain, concurrent with the use of buprenorphine for addiction treatment in primary care, have paralleled the increased misuse, abuse, and diversion of these two medications.
Disclosure

Denver Health—Rocky Mountain Poison & Drug Center (RMPDC) operates the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System and provides data to industry, regulatory agencies and researchers on a subscription basis. RMPDC employees only receive their salary for their participation in system operations and research activities.

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