Determinants of Increased Opioid-Related Mortality in the United States and Canada, 1990–2013: A Systematic Review

We review evidence of determinants contributing to increased opioid-related mortality in the United States and Canada between 1990 and 2013.

We identified 17 determinants of opioid-related mortality and mortality increases that we classified into 3 categories: prescriber behavior, user behavior and characteristics, and environmental and systemic determinants. These determinants operate independently but interact in complex ways that vary according to geography and population, making generalization from single studies inadvisable. Researchers in this area face significant methodological difficulties; most of the studies in our review were ecological or observational and lacked control groups or adjustment for confounding factors; thus, causal inferences are difficult.

Preventing additional opioid-related mortality will likely require interventions that address multiple determinants and are tailored to specific locations and populations. (*Am J Public Health*. Published online ahead of print June 12, 2014: e1–e11. doi:10.2105/AJPH.2014.301966)

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DURING THE PAST 2 DECADES, mortality resulting from unintentional prescription drug overdoses has risen steeply in the United States and Canada and is now widely recognized as a major public health problem. Deaths involving prescription opioid analgesics, including hydrocodone, oxycodone, hydromorphone, and methadone, have surpassed deaths from heroin and cocaine combined.[1] In 2010, the 11th consecutive year in which drug overdose deaths increased, 75% of all pharmaceutical overdose deaths involved opioids, and prescription opioids were involved in 16 651 deaths in the United States, a more than 4-fold increase since 1999.[2–4] Although national data are unavailable for Canada, in Ontario opioid-related mortality doubled between 1991 and 2007, and by 2004 it was more than double the HIV/AIDS mortality rate (27.2 vs 12 per million).[5]

Although this problem is most acute in North America, it has the potential, amid calls to increase worldwide access to opioids,[6–8] to become a serious global health problem. Identifying the determinants of increased mortality is an essential step in reducing opioid-related deaths in the United States and Canada and curbing future increases worldwide. However, although much has been written about this phenomenon, the evidence base is fragmented and complex, extant reviews are unsystematic and idiosyncratic,[9–11] and media coverage is often highly sensationalized. Our aim was to systematically identify and review evidence regarding determinants of increased opioid-related mortality in the United States and Canada between 1990 and 2013.

METHODS

In collaboration with a research librarian, we searched 3 electronic databases—Ovid MEDLINE (1946 through week 4 of September 2013) and MEDLINE In-process and Other Non-Indexed Citations, EMBASE (1988 through week 4 of September 2013), and ProQuest ABI/INFORM Complete (1990 through week 4 of September 2013)—for articles published between January 1990 and September 2013 using the following keywords: "opiate alkaloids," "opiate," "opioid," and "opioid-related disorders" in conjunction with "mortality," "fatal," "death," and "inappropriate prescribing." Also, we hand searched reference lists of relevant articles to identify additional publications (details on the full search strategy are provided in Appendix 1, available as a supplement to the online version of this article at http://www.ajph.org).

We included English-language original research studies that provided quantitative evidence of 1 or more determinants of increased opioid-related mortality in the United States or Canada between January 1990 and September 2013. We excluded case histories, commentaries, editorials, reviews, and articles that did not provide original evidence of determinants of opioid-related mortality.

Two of the authors independently assessed all titles and abstracts for inclusion and then assessed the full text of considered studies. All disagreements were resolved through discussions with the first author, who had final say on inclusion.

We developed a standardized data extraction form that was piloted on 10 articles and subsequently revised. Two authors independently extracted the following information from the articles: name of first author, geographic setting, declaration of competing interests, prescription opioid drugs discussed, and determinants of increased prescription opioid mortality. One of the authors extracted the study type for all articles. Again, all disagreements were resolved through discussions with the first author, who had final say on data extraction.

RESULTS

Our initial searches produced 3142 unduplicated titles. After title and abstract reviews, 144 articles remained for a full text review. After this review, 47 articles remained for inclusion (Figure 1): 26 time-series articles, 10 case-series articles, 4 case–control articles, 3 cross-sectional articles, 1 case–cohort article, 1 observational cohort article, and 2 mixed-methods articles. Table 1

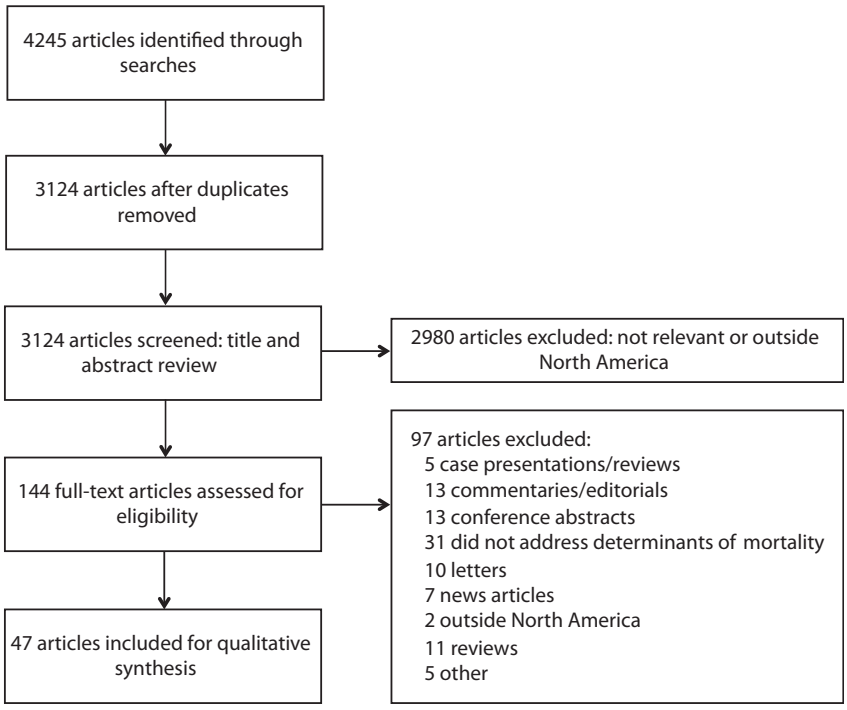

FIGURE 1—Flow diagram of systematic review.

provides a summary of each study included.[12–56] We could not identify a competing interest declaration in 21 of the articles; among the remainder, 24 declared none, and 2 declared some competing interest.

Our sample identified evidence for 17 determinants of increased opioid-related mortality in the United States and Canada between 1990 and 2013. For conceptual clarity, we grouped these determinants into 3 broad categories: prescriber behavior, user behavior and characteristics, and environmental and systemic determinants (Table 2).

The most commonly identified determinants were user behavior and characteristics, particularly demographic characteristics and polydrug toxicity, and prescriber behavior, primarily increases in opioid prescriptions and dosages and prescriptions for oxycodone and methadone in particular. Note, however, that a greater number of studies does not imply stronger evidence.

DISCUSSION

We found a complex, multifaceted, and geographically varied web of determinants of increased opioid-related mortality.

Prescriber Behavior

Our review identified 5 ways in which the behavior of opioid prescribers may have played a role in increased opioid-related mortality: prescribing more opioids, prescribing higher doses of opioids, prescribing oxycodone, prescribing methadone, and prescribing at high volumes.

Prescription and sales of opioids. Since the early 1990s, prescription and sales of opioid analgesics have risen steeply. Between 1999 and 2010, sales of prescription painkillers to US hospitals, clinics, and pharmacies increased 4-fold, with an accompanying increase in opioid-related mortality.[2] The number of opioid prescriptions dispensed from US retail pharmacies increased from 174.1 million in 2000 to 256.9 million in 2009.[57] In 2006, Americans consumed 115 272 kilograms of opioids, more than twice as much as in 1997[10]; in Canada, prescription opioid consumption doubled between 2000 and 2010.[58] In 2008, a Utah Department of Health survey showed that 21% of adults had been prescribed an opioid pain medication in the preceding 12 months.[59]

Prescription of opioid analgesics for chronic noncancer pain in particular has increased.[12] Between 1980 and 2000, US prescriptions of opioids for chronic musculoskeletal pain doubled, and rates for more potent opioids quadrupled.[13] According to one estimate, 9.6 million to 11.5 million adults were on long-term opioid therapy in the United States during 2005.[60]

We found 8 studies[1,2,14–19] providing evidence that increased prescriptions for opioids may have played a role in increased opioid-related mortality. Canadian studies showed correlations between mortality and consumption of 4 prescription opioids (fentanyl, morphine, oxycodone, and hydromorphone) in 2 provinces[1] and correlations between opioid prescribing rates and mortality rates across Ontario counties.[14] Similarly, in a study of North Carolina counties, there were correlations between opioid sales, emergency department visits for overdoses, and opioid-related mortality.[16] A US study also demonstrated a state-level association between overall opioid consumption and drug poisoning mortality.[17]

Opioid dosage. As overall opioid prescriptions have increased, so too have prescribed dosages. For example, a study of workers' compensation claims in the state of Washington showed that the average daily morphine-equivalent dose (MED) of long-acting opioids increased 50% between 1996 and 2002 and exceeded the recommended "red flag" dose by 2005.[13]

We found 7 studies[5,12,20–24] providing evidence of the contribution of increased dosages to increased opioid-related mortality. A study of social assistance recipients in Ontario showed that, between 2003 and 2008, there were increases in the mean daily doses of oxycodone (increase of 27.4%) and fentanyl (increase of 14.2%) dispensed, whereas doses remained flat for other opioids.[21] By 2008, one third of prescriptions for long-acting

TABLE 1—Summary Information for All of the Studies in the Final Sample: Review of Opioid-Related Mortality in the United States and Canada, 1990–2013

Author	Year	Journal	Type of Study	Setting	Declared Competing Interest	Prescriber Behavior	User Behavior and Characteristics	Environmental and Systemic Factors
Albion et al.[28]	2010	*American Journal of Forensic Medicine and Pathology*	Case series	Ontario	NA		X	
Bohnert et al.[20]	2011	*Journal of the American Medical Association*	Case–cohort	US	No	X	X	
CDC[29]	2005	*Morbidity and Mortality Weekly Report*	Time series	Utah	NA		X	
CDC[30]	2009	*Morbidity and Mortality Weekly Report*	Time series	Washington State	NA		X	
CDC[2]	2011	*Morbidity and Mortality Weekly Report*	Time series	USA	NA	X		X
CDC[31]	2012	*Morbidity and Mortality Weekly Report*	Time series	US	NA	X		X
CDC[38]	2013	*Morbidity and Mortality Weekly Report*	Time series	US	NA		X	
Cerda et al.[39]	2013	*Drug and Alcohol Dependence*	Time series	New York City	No		X	X
Dasgupta et al.[55]	2009	*PLoS One*	Time series	US	Yes			X
Dhalla et al.[5]	2009	*Canadian Medical Association Journal*	Time-series/administrative linkage	Ontario	No			
Dhalla et al.[37]	2011	*Canadian Family Physician*	Cross-sectional individual	Ontario	No	X		
Dunn et al.[12]	2010	*Annals of Internal Medicine*	Observational cohort	Washington State	Yes	X	X	
Fischer et al.[1]	2013	*Pharmacoepidemiology and Drug Safety*	Time series	British Columbia, Ontario	No	X		
Franklin et al.[13]	2005	*American Journal of Industrial Medicine*	Time series	Washington State	NA			X
Franklin et al.[25]	2012	*American Journal of Industrial Medicine*	Time series	Washington State	NA			X
Gomes et al.[14]	2011	*Healthcare Quarterly*	Cross-sectional ecological	Ontario	NA	X		
Gomes et al.[22]	2011	*Archives of Internal Medicine*	Case–control	Ontario	No	X		
Gomes et al.[21]	2011	*Open Medicine*	Time series, cross sectional	Ontario	No	X		
Green et al.[15]	2011	*Drug and Alcohol Dependence*	Time series	Connecticut	No		X	
Hall et al.[32]	2008	*Journal of the American Medical Association*	Case series	West Virginia	No	X	X	
Johnson et al.[51]	2011	*Pain Medicine*	Pre/post, time series	Utah	No			X
Johnson et al.[40]	2012	*Journal of General Internal Medicine*	Case series	Utah	No		X	
Lanier et al.[26]	2012	*Pain Medicine*	Case–control	Utah	No	X	X	
Ling[47]	2013	*Canadian Journal of Addiction Medicine*	Time series	Nova Scotia	NA		X	
Madadi et al.[23]	2013	*PLoS One*	Case series	Ontario	No	X	X	
Madden and Shapiro[33]	2011	*American Journal of Forensic Medicine and Pathology*	Case series	Vermont	NA	X	X	
Modarai et al.[16]	2013	*Drug and Alcohol Dependence*	Time series	North Carolina	No	X		X
Mueller et al.[41]	2006	*American Journal of Preventive Medicine*	Time series	New Mexico	No		X	
Ogle et al.[42]	2012	*Forensic Science International*	Case series	Florida	NA		X	
Paulozzi et al.[43]	2006	*Pharmacoepidemiology and Drug Safety*	Time series	US	NA		X	
Paulozzi[27]	2006	*American Journal of Public Health*	Time series	US	NA	X		
Paulozzi and Ryan[17]	2006	*American Journal of Preventive Medicine*	Cross-sectional ecological	US	NA	X		X

Continued

TABLE 1—Continued

Paulozzi and Xi[50]	2008	*Pharmacoepidemiology and Drug Safety*	Time series	US	No			X
Paulozzi et al.[34]	2009	*Addiction*	Case series	West Virginia	No	X	X	
Paulozzi and Stier[54]	2010	*Journal of Public Health Policy*	Time series	New York State, Pennsylvania	NA			X
Paulozzi et al.[53]	2011	*Pain Medicine*	Time series	US	No			X
Paulozzi et al.[24]	2012	*Pain Medicine*	Case–control	New Mexico	No	X	X	
Peirce et al.[48]	2012	*Medical Care*	Case–control	West Virginia	No		X	
Piercefield et al.[18]	2010	*American Journal of Preventive Medicine*	Time series	Oklahoma	No	X	X	X
Shah et al.[36]	2005	*Addiction*	Time series	New Mexico	NA		X	
Shah et al.[45]	2008	*Addiction*	Time series	New Mexico	NA		X	
Shah et al.[44]	2012	*Drug and Alcohol Dependence*	Time series	New Mexico	No		X	
Sims et al.[19]	2007	*Journal of Biomedical Informatics*	Time series	Utah	NA	X	X	
Tormoehlen et al.[49]	2011	*Clinical Toxicology*	Case series	Indiana	No			X
Walley et al.[52]	2013	*British Medical Journal*	Interrupted time series	Massachusetts	No			X
Weimer et al.[35]	2011	*Journal of Addiction Medicine*	Case series	Virginia	NA	X	X	
Wunsch et al.[46]	2009	*American Journal on Addictions*	Case series	Virginia	NA		X	

Note. CDC = Centers for Disease Control and Prevention; NA = no competing interest declaration identified. An X indicates that the study reports evidence regarding the determinant.

oxycodone exceeded clinical guidelines with respect to mean daily dose,[21] and patients receiving higher doses had higher rates of overdose, opioid-related mortality, and all-cause mortality.[21,22]

A study of patients receiving opioids for chronic noncancer pain in a health maintenance organization in Washington State also showed that the risk of overdose increased with increased dosages.[12] It was noted in this study that, although overdose risk was higher at high doses, most overdoses occurred at low to moderate doses because such doses are prescribed more frequently, suggesting that even the most frequently used dose regimens carry some risk.

The importance of increased dosages is supported by evidence indicating a dose–response relationship between maximum daily prescribed dose and risk of death.[12,20,22,24] However, there does not seem to be an evidence-based threshold for what constitutes a dangerously high dose. Although some clinical guidelines suggest an MED of 200 milligrams per day as a “watchful dose,” studies in our sample showed overdose and mortality increases at doses ranging from 40 to 200 milligrams per day MED.[12,20,22,24]

Prescription of oxycodone. Prescription of more potent opioids, particularly methadone and long-acting formulations of oxycodone, has increased most rapidly, with associated increases in mortality. Before 1990, weaker opioids such as codeine and meperidine were used more frequently than stronger formulations.[17] Between 1997 and 2006, US retail sales of methadone increased 1177%, sales of oxycodone increased 732%, and sales of fentanyl increased 479%, whereas sales of hydromorphone, hydrocodone, and morphine increased between 196% and 274% and sales of codeine and meperidine dropped 25% and 28%, respectively.[10]

Studies of workers' compensation claims in Washington State between 1996 and 2002 showed that whereas overall opioid prescriptions increased 25%, prescriptions for the more potent Schedule II opioids increased by almost 250%, with an accompanying increase in opioid-related mortality.[13,25] Similarly, a North Carolina study demonstrated significant increases in prescriptions of oxycodone (839%), methadone, (607%) and fentanyl (530%) and significant decreases in prescriptions of meperidene and codeine between 1997 and 2010.[16]

We found 7 studies[5,17,18,21,23,26,27] that provided evidence for the contribution of prescription of oxycodone, particularly the long-acting formulation OxyContin, to increased opioid-related mortality. Long-acting opioids such as OxyContin may be particularly dangerous when used recreationally: crushing pills releases high doses of the drug, and repeated use to increase or maintain a narcotic effect may lead to overdose. In addition, recreational users may avoid formulations that include opioids along with acetaminophen because of hepatoxicity.[17]

A study of patients in the Ontario public drug plan between 2003 and 2008 showed that whereas prescription rates for long-acting oxycodone more than doubled, rates for all other opioids decreased or remained flat, and opioid-related mortality increased.[21] Other Ontario studies showed that annual opioid-related mortality rates increased 41% and oxycodone-related mortality increased 416% after OxyContin was added to the provincial drug formulary[5] and that oxycodone

TABLE 2—Determinants of Increased Opioid-Related Mortality: United States and Canada, 1990–2013

Determinant	No. of Studies[a]
Prescriber behavior	
High-volume prescribing[37]	1
Opioid prescription or sales[1,2,14–19]	8
Opioid dosage[5,12,20–24]	7
Prescription of oxycodone[5,17,18,21,23,26,27]	7
Prescription of methadone[17–19,26–36]	14
User behavior and characteristics	
History of substance abuse[32,34,40,42]	4
Diversion[23,26,32–35]	6
Doctor or pharmacy shopping[23,24,32,40,48]	5
Drug substitution[15,43]	2
Polydrug toxicity[12,15,18,24,28,30,33–35,41,42,46–48]	14
Sociodemographic characteristics[2,12,15,18–20,24,26,28–30,32,36,38–46]	22
Environmental and systemic determinants	
Area urbanization or socioeconomic status[2,16,32,39,50]	5
Geography[2,17]	2
Guidelines, policies, and consensus statements[5,13,25,31,49]	5
Interventions[51,52]	2
Media coverage[55]	1
Prescription drug monitoring programs[53,54]	2

[a]Number of studies in sample reporting evidence regarding determinant.

was involved in one third of all opioid-related deaths between 2006 and 2008.[23]

Prescription of methadone. We found 14 studies[17–19,26–36] that provided evidence for the contribution of methadone prescriptions to increased opioid-related mortality. Methadone's unusual pharmacology poses particular challenges because of the small difference between therapeutic and toxic doses.[34] There is also some evidence that prescribers may prefer methadone for economic rather than clinical reasons. Because methadone is a cheaper generic drug, private insurers, Medicaid, and individual clinicians may prefer it over more expensive, patent-protected alternatives, thus driving increases in methadone prescriptions.[30,34,57]

There is evidence that a high proportion of opioid-related deaths have involved methadone. Studies conducted in Washington State,[30] Oklahoma,[18] and West Virginia[32] have shown that methadone is involved in higher numbers of deaths than any other opioid, and a US study revealed that methadone was involved in twice as many single-drug deaths as any other opioid.[31] A US ecological study conducted in 2002 suggested that methadone (43%) and oxycodone (46%) explained a large proportion of the geographic variation in opioid-related mortality.[17]

Although methadone has traditionally been prescribed to combat substance abuse in methadone maintenance programs, it is increasingly being used for its original purpose, pain relief. We found some evidence that the use of methadone for pain relief has played a role in increased mortality. A Vermont study showed that although the percentage of drug overdose deaths that were methadone related increased from 12% to 37% between 2001 and 2006, only 2 of 76 decedents were in a methadone maintenance program.[33]

A Utah study showed that, between 1997 and 2004, population-adjusted methadone prescription rates increased 727% and opioid-related mortality increased 1770%. During this period, rates of heroin abuse and admissions to substance abuse facilities remained unchanged, suggesting that the increased prescriptions and associated mortality resulted primarily from prescriptions for pain.[19] By contrast, a New Mexico study revealed a slight decrease in methadone-related deaths between 1998 and 2002 and a higher proportion of decedents with prescriptions related to methadone maintenance (45%).[36]

High-volume prescribing. The possible contribution of high-volume prescribing to opioid-related mortality has received considerable attention in the media[61] and scholarly literature.[2,57] Some states report problems with so-called "pill mills," which prescribe large quantities of opioids to patients with questionable diagnoses.[2] We found 1 study[37] providing evidence that high-volume prescribing may have played a role in increased opioid-related mortality. A study of Ontario family physicians showed that the top quintile of prescribers issued opioid prescriptions 4.5 times more frequently than the next quintile and wrote the final opioid prescription in 63% of opioid-related deaths. However, it is still unclear whether high-volume prescribing is a direct driver of increased mortality.

User Behavior and Characteristics

Our review identified 6 ways in which opioid analgesic users may have contributed to increased opioid-related mortality, either through behaviors (e.g., diversion, doctor or pharmacy shopping, polydrug use, or drug substitution) or characteristics (e.g., sociodemographic characteristics or history of substance abuse) that increased their risk of opioid-related death. Although we found evidence that user behaviors and characteristics contribute to risk of opioid-related mortality, in most cases their exact contribution to increased mortality was unclear.

Sociodemographic characteristics. Opioid-related mortality trends have been marked by considerable sociodemographic differences. We found 22 studies[2,12,15,18–20,24,26,28–30,32,36,38–46] that examined the contribution of sociodemographic characteristics, including race/ethnicity, gender, age, socioeconomic status (SES), and rural–urban residence, to increased opioid-related mortality. In general, opioid-related mortality rates have been higher among men, non-Hispanic Whites and American Indian/Alaska Natives, middle-aged individuals, those living in rural areas, and those of lower SES.

However, we found considerable heterogeneity amid these general patterns. For example, studies conducted in Utah,[29,45] New Mexico,[41] and Oklahoma[18] showed that although men were more likely to overdose, relative increases in opioid-related mortality were greater among women. This trend was also seen nationally: opioid-related mortality increased 415% among women and 265% among men between 1999 and 2010.[38]

Several studies have noted that demographic trends vary over

time and according to specific drug. For example, a New York City study revealed that whereas methadone-related deaths were higher among Blacks than Whites in 1990, this trend had reversed by 2006. The authors suggested that this situation may have reflected the shift in methadone prescriptions from substance abuse treatment to treatment of pain.[39] A Connecticut study showed that individuals who overdosed on illicit drugs or methadone were younger, less likely to be male and White, and less likely to live in rural areas than individuals who overdosed on other prescription opioids.[15]

Polydrug toxicity. Many decedents are found with prescription medications (particularly benzodiazepines and other sedatives–hypnotics, antidepressants, and sleep aids), alcohol, or illicit drugs, along with 1 or more prescription opioids, in their bloodstreams. We found 14 studies[12,15,18,24,28,30,33–35,41,42,46–48] providing evidence that polydrug toxicity may have played a role in increased opioid-related mortality. Evidence suggests that increased opioid-related mortality might be characterized as part of an epidemic of polydrug mortality.

Among methadone-related decedents in western Virginia, 61% died from polydrug toxicity, with an average of 3 substances identified.[35] In Ontario, 25 of 45 methadone-related decedents had other drugs in their systems, including 18 with diazepam.[28] A Virginia study of opioid-related deaths revealed that a majority of cases involved more than 1 medication or drug, and 73% involved benzodiazepines or antidepressants.[46] Studies conducted in Washington[30] and West Virginia[34,48] also showed that significant proportions of opioid-related deaths involved other drugs, particularly benzodiazepines and antidepressants.

Diversion. There is substantial evidence of diversion—defined as "the act of redistributing a drug to individuals for whom it was not prescribed, regardless of the receiving party's motive"[62(p308)]—of prescription opioids. Sources of diverted opioids include individuals who have received prescriptions for pain or, less commonly, have been allowed "carries" (doses that do not have to be consumed under observation and can be taken home) from methadone maintenance programs.[28]

We found 6 studies[23,26,32–35] providing evidence that diversion may have played a role in increased opioid-related mortality. Diversion is associated with an increased risk of opioid-related mortality, but rates vary according to location, gender, age, and type of drug. Studies in our review demonstrated that 63% of all unintentional drug poisoning decedents in West Virginia,[32] two thirds of methadone-related decedents in Vermont[33] and western Virginia,[35] 56% of methadone-related deaths in Ontario, and 40% of opioid-related deaths in Utah[26] showed evidence of diversion. By contrast, an Ontario study revealed evidence of diversion in only 7% of opioid-related deaths between 2006 and 2008.[23]

Because access to a recent prescription does not rule out the possibility that a decedent obtained the opioid dose that contributed to his or her death through diversion, the role of diversion at the population level is often inferred from a mismatch between the demographic profiles of legitimate patients and decedents. For example, in studies in Utah[19] and West Virginia,[34] the age profile of methadone decedents more closely resembled that of individuals with illicit drug overdoses as opposed to methadone prescriptions.

Similarly, a study of unintentional poisonings in the United States between 1990 and 2002 noted that the gender and age distributions (male and middle aged) of decedents matched those of individuals whose deaths were caused by drugs of abuse rather than individuals who suffered from chronic noncancer pain, who tend to be female and older.[17] However, although there is evidence that diversion is a determinant of mortality, it is still unclear whether rates of diversion have changed during the past 2 decades and thus are a direct driver of increased mortality.

Doctor or pharmacy shopping. The practices of doctor shopping (visiting multiple physicians to obtain prescriptions) and pharmacy shopping (visiting multiple pharmacies to fill prescriptions) for prescription opioids have received considerable attention.[63] We found 5 studies[23,24,32,40,48] providing evidence that doctor or pharmacy shopping may have played a role in increased opioid-related mortality. A New Mexico study showed that risk of overdose increased with increasing numbers of prescriptions, prescribers, and pharmacies visited, with pharmacies showing the strongest association.[24] According to a West Virginia study, the percentages of doctor shoppers (25.2% vs 3.6%) and pharmacy shoppers (17.5% vs 1.3%) were significantly higher among opioid-related decedents than among living recipients of opioid prescriptions.[48]

Rates of doctor shopping may vary according to location, age, and gender. For example, a study conducted in West Virginia[32] revealed evidence of doctor shopping among 21% of decedents, and doctor shopping was more common among women and those aged 35 to 44 years. By contrast, an Ontario[23] study showed evidence of doctor shopping in 2% of decedents.

Although some[64,65] worry that the availability of opioids on the Internet might contribute to doctor or pharmacy shopping, we found no evidence that this is a substantial determinant of opioid-related mortality. Surveys have shown that only 0.4% of adults and 1% of young people of high school age in the United States obtain narcotics on the Internet.[57]

History of substance abuse. We found 4 studies providing evidence that a history of substance abuse[32,34,40,42] may have played a role in increased opioid-related mortality. A study of methadone-related deaths in West Virginia showed that almost all of the deaths involved individuals who were current or former substance abusers.[32,34] A qualitative study of decedents in Utah revealed that a health care provider had expressed concern about abuse of opioids in a third of the cases, and contacts or next of kin reported substantial rates of overconsumption, recreational use, and self-medication.[40]

Drug substitution. Because prescription medications carry a veneer of safety and legitimacy and lack the stigmatization that accompanies illicit drugs, individuals may be more likely to initiate or experiment with them.[15,66] We found 2 studies[15,43] providing evidence that such drug substitution may have played a role in increased prescription opioid-related mortality. A Connecticut study showed that between 1997 and 2007, deaths from prescription

opioids increased, whereas deaths from heroin decreased.[15] By contrast, a US study noted that poisoning deaths from prescription opioids and illicit drugs have increased concurrently, although this investigation could not exclude substitution as a possibility.[43]

Environmental and Systemic Determinants

Our review identified 6 environmental and systemic determinants that may have contributed to changes in opioid-related mortality: guidelines, policies, and consensus statements; area urbanization or SES; geography; interventions; prescription drug monitoring programs (PDMPs); and media coverage. In many cases, these determinants may have influenced the behavior of physicians and users, including behaviors identified in previous sections.

Guidelines, policies, and consensus statements. Many articles have emphasized the impact of changes in pain management philosophy and practice, as physicians were encouraged not to allow fears of abuse, addiction, and adverse effects to interfere with their prescribing opioids[43] and to prescribe stronger analgesics for chronic noncancer pain.[30] Since the early 1990s, patient advocacy groups and professional organizations have lobbied for increased use of opioids to treat pain,[55] which has led to the implementation of guidelines, policies, and consensus statements endorsing expanded prescription of opioids.[32] In 1997, the American Academy of Pain Medicine and the American Pain Society issued a joint consensus statement,[67] and the American Society of Anesthesiologists issued practice guidelines,[68] endorsing use of opioids for chronic pain. In the following decade, US consumption of methadone, oxycodone, and hydrocodone increased 13-, 9-, and 4-fold, respectively.[32]

We found 5 studies[5,13,25,31,49] providing evidence that guidelines, policies, and consensus statements may have played a role in increased opioid-related mortality. An Indiana study showed increases in the number of calls to a poison control center involving adolescents and opioids, as well as the number of medical complications and deaths related to opioids, during the 7 years after the release of the 2000 Joint Commission on Accreditation of Healthcare Organizations pain standards, which made adequate pain management a clinical performance measure. All 15 deaths in the study occurred after the release of these standards.[49]

A study of workers' compensation claims in Washington State revealed a shift from Schedule III/IV to Schedule II opioids, an increased average dose of long-acting opioids, and increased opioid-related mortality during the 6 years after the 1996 release of guidelines that reversed the state policy limiting use of opioids for chronic pain.[13] A follow-up study showed declines in total numbers of prescriptions, the proportion of claimants receiving opioids, dosages, and eventually opioid-related mortality following the introduction of a new guideline in 2007 that included a "yellow flag" warning dose threshold of 120 milligrams per day MED.[25]

More recently, a US study provided evidence suggesting that federal regulations may have affected the country's methadone-related mortality trends.[31] In November 2006, the Food and Drug Administration issued warnings about the careful prescribing of methadone and revised the interval for the recommended starting dosage; in addition, in January 2008, at the request of the Drug Enforcement Administration, manufacturers limited distribution of the largest methadone formulation (40 mg). Methadone-related mortality peaked in 2007 and then decreased in 2008 and 2009, paralleling the decrease in the amount of methadone distributed.

Area urbanization or socioeconomic status. We found 5 studies[2,16,32,39,50] providing evidence that area urbanization or SES may have played a role in increased opioid-related mortality. A US study showed substantial variation and change over time in the spatial patterning of opioid-related mortality: in 1999, large central metropolitan areas had the highest opioid-related mortality rates, and noncore areas had the lowest rates; by 2004, noncore areas had the highest rates and had seen the largest relative increase during that time period.[50]

A spatial analysis in New York City also showed that clustering of opioid-related mortality changed over time and varied according to type of drug. Although methadone-related fatalities were concentrated in neighborhoods with high income inequality, high poverty rates, and lower median incomes from 1990 to 2006, the clustering of other opioid-related fatalities shifted during this period and, by 2000, was concentrated in neighborhoods with high income inequality but lower poverty rates.[39] A spatial analysis of North Carolina counties in 2010 revealed that opioid sales and overdoses were more frequent in rural than urban counties.[16]

Geography. We found 2 studies[2,17] providing evidence that geographic factors may have played a role in increased opioid-related mortality. A US study showed that drug poisoning mortality rates varied 8-fold between states, as did opioid consumption (methadone, 13-fold; oxycodone, 7-fold; overall, 4-fold).[17] Another study showed that prescription opioid sales ranged from 3.7 (Illinois) to 12.6 (Florida) kilograms per 10 000 population, and opioid-related mortality rates ranged from 5.5 (Nebraska) to 27 (New Mexico) per 100 000 population.[2] The exact causes of these geographic variations are unclear.

Interventions. Recently, several jurisdictions have implemented interventions targeted at reducing opioid-related mortality. We found 2 studies[51,52] providing evidence that interventions may have played a role in opioid-related mortality trends. A Massachusetts study showed that implementation of overdose education and naloxone distribution programs in communities significantly reduced fatal overdose rates while having no effect on nonfatal overdoses.[52] Another study in Utah noted that, in the 2 years following implementation of the state's Prescription Pain Medication Program (which consisted of a media campaign and revised clinical guidelines), there was a 14% drop in opioid-related deaths, although this evidence was suggestive rather than definitive.[51]

Prescription drug monitoring programs. Beginning in 2002, many states implemented prescription drug monitoring programs, which collect prescription and dispensation information for controlled substances.[57] We found 2 studies[53,54] providing evidence that PDMPs may have played a role in opioid-related mortality trends. In theory, PDMPs should reduce the overall

availability of opioids by discouraging doctor shopping and high-volume prescribing. However, the evidence is mixed. One study suggested that New York State's lower opioid mortality relative to that of Pennsylvania might be due to a stricter and better-funded PDMP.[54] However, a national observational study revealed no correlation between PDMPs and mortality or prescription rates.[53] An additional study noted that, given the minimal amount of evidence of doctor shopping for methadone, PDMPs may be of limited use for predicting risk of overdose.[35]

Media coverage. The increase in opioid-related mortality has received considerable media coverage, which may in turn have had an impact on mortality rates. We found 1 study[55] providing evidence that media coverage may have played a role in increased opioid-related mortality. A time-series analysis showed that increased media coverage of opioids preceded increased rates of opioid poisoning mortality by 2 to 6 months and accounted for 88% of the variation in mortality.[55] The authors speculated that coverage often amounted to "inadvertent endorsements of prescription drug abuse," thus increasing the popularity of opioids. Several studies have also speculated that increased media coverage may lead to "diagnostic suspicion bias," as medical examiners and coroners screen more carefully for opioids as a cause of death or report poisoning at lower blood levels,[27,43,55] although another study revealed little evidence of such practices.[50]

Quality of Evidence and Methodological Challenges

The majority of studies in our review were ecological or observational and lacked control groups or adjustment for confounding factors, making inference of causation between determinants and opioid mortality difficult. We found few investigations with a study design adequate to identify specific causes of opioid-related mortality increases in any geographic region. In our sample, only 5 of the 47 studies[5,16,49,52,55] were explicitly designed to provide quantitative evidence that a particular determinant was associated with increases in opioid-related mortality. We found many more studies that, although framed by discussions of mortality increases, examined determinants of mortality rather than mortality increases and suggested possible causes of such increases. Further research on the exact causes of opioid-related mortality increases is needed.

Researchers have noted a number of other methodological challenges. Determining exact cause of death is often difficult,[11,62,69] particularly in cases involving methadone.[69] Prescription data are proprietary, and data on adverse events are held privately.[57] There is some inconsistency in *International Classification of Diseases* codes for drug poisoning, as well as a lack of standardization in drug categorization and terminology[57] and coroners' reports.[36,55] Identification of diversion and doctor shopping is particularly difficult because it generally relies on interviews with contacts or on proxies such as having a prescription in the preceding 30 days.

Generalizing from specific studies to national trends or cross-national comparisons seems inadvisable given the population and regional variation in determinants of opioid-related mortality we found across studies. As noted, the contribution of determinants such as doctor shopping, diversion, and sociodemographic characteristics to opioid-related mortality may vary considerably across space, over time, and between populations. Despite these variations, we have observed cases in the literature in which data from several local studies are combined and presented as if they were nationally representative.[56]

Although we classified determinants into 3 categories for conceptual clarity, we should note that they may interact and mutually influence one another. For example, changes in guidelines, policies, or regulations may influence the quantity and dosage of opioids prescribed.[25,32] Similarly, increased opioid prescriptions combined with a lack of physician training may lead to increased opioid diversion,[33,41] and media coverage of opioid-related mortality may influence and be influenced by the behaviors of physicians and users.[49,55]

The increase in opioid-related mortality has been marked by wide sociodemographic inequalities,[2] but our review revealed surprisingly little evidence regarding causes of these patterns. For example, we found no studies focusing on specific causal factors for the wide racial/ethnic differences in opioid-related mortality, although some did note that these differences match the pattern for medical and nonmedical use of opioid pain relievers,[2] an observation that is supported by research on racial/ethnic inequalities in pain management.[70–74] Further research into the causes of sociodemographic inequalities in opioid-related mortality is needed.

Limitations

Our study had several limitations. First, we did not perform a formal quality assessment of the articles. Second, conducting a search with different search terms or similar terms in different databases can yield a different sample of articles. Consultation with a reference librarian improved our ability to capture relevant studies, but it is possible that some articles were missed. Third, we used broad inclusion and exclusion criteria to capture the largest possible number of studies, necessitating substantial discretionary judgment. Our title review and extraction of data in duplicate reduced but did not entirely eradicate this potential bias. As with any review, limitations of the review methodology should be considered when interpreting the results.

Conclusions

To our knowledge, this is the first systematic review of the determinants of opioid-related mortality in North America. Our review identified a diverse and regionally variable set of determinants of increased opioid-related mortality in the United States and Canada during the past 2 decades, including prescriber behaviors, user behaviors and characteristics, and environmental and systemic determinants. These determinants operate independently but interact in complex ways that vary according to time, geography, and population.

A number of commentaries, editorials, and reviews have argued that phenomena not discussed in this review—including prescriber error and lack of training[11,57,75] and patient error and nonadherence[11]—have been significant determinants of increases in opioid-related mortality. We found no evidence to support these claims. However, absence of evidence should not be taken to imply evidence of absence.

Our review identified significant limitations in the evidence base for determinants of increased opioid-related mortality. Researchers in this area face substantial methodological hurdles. Few studies in our sample had a study design adequate for robust causal inference or tested the sensitivity of their results to methodological choices, and most studies focused on small populations or geographic areas. Researchers and decision-makers should exercise caution in drawing larger generalizations from this work, and further research on the exact causes of mortality increases and inequalities in different populations is needed.

To date, US federal government efforts to reduce opioid-related mortality have emphasized monitoring and securing the supply of scheduled drugs,[76] as well as implementing prescriber and patient education programs through the Food and Drug Administration's risk evaluation and mitigation strategy.[77] Our review of the evidence suggests that a more multifaceted response is warranted. Although some recommend focusing on single factors such as physician competence[11] or user mental health,[78] curbing opioid-related mortality will likely require novel, multisectoral public health approaches that address multiple determinants of increased mortality.[79,80]

Widespread mortality from prescription opioids currently appears to be restricted to North America. However, although consumption of opioid analgesics has increased sharply in the United States and Canada, untreated pain remains prevalent worldwide, and global inequalities in opioid availability are widespread and well documented. Without access to adequate pain management, 600 million people alive today are likely to experience negative health effects caused by untreated pain.[8] Canada and the United States rank first and second in per capita opioid use, together consuming the majority of global supplies of hydrocodone (99.9%), oxycodone (87.3%), morphine (60.1%), and methadone (51.8%).[81] By contrast, strong opioids are unavailable in more than 150 countries,[82] and, when they are available, they often cost more in low- and middle-income countries.[8,83] An estimated 5.5 billion people live in countries with little or no access to opioids, and global opioid consumption would increase 6-fold if all countries had adequate access.[84]

Given these global inequalities, many have called for increased worldwide access to effective pain management, particularly opioid analgesics.[7,8,83,85–89] Addressing the global burden of untreated pain and improving access to opioids in resource-poor settings are top priorities. However, our review indicates that improved opioid access worldwide, particularly for chronic noncancer pain, could in some cases lead to increased opioid-related mortality. Given the evidence of the role of diversion in opioid-related mortality, we might expect some proportion of these deaths to occur as "collateral damage" among individuals without legitimate prescriptions. We encourage clinicians, public health officials, and policymakers to consider evidence-based prevention efforts, tailored to different populations and geographic areas, as a complement to increased access to opioids. ■

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N. B. King and S. Harper originated the study. N. B. King, V. Fraser, C. Boikos, and R. Richardson performed the searches, review, and data extraction. All of the authors contributed to writing and revising the article.

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Human Participant Protection

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