Worldwide Prevalence and Trends in Unintentional Drug Overdose: A Systematic Review of the Literature

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Background. Drug overdose is an important, yet an inadequately understood, public health problem. Global attention to unintentional drug overdose has been limited by comparison with the scope of the problem. There has been a substantial increase in drug overdose incidence and prevalence in several countries worldwide over the past decade, contributing to both increased costs and mortality.

Objectives. The aim of this study was to systematically synthesize the peer-reviewed literature to document the global epidemiological profile of unintentional drug overdoses and the prevalence, time trends, mortality rates, and correlates of drug overdoses. We searched different combinations of Medical Subject Headings (MeSH) terms in PubMed for articles published from 1980 until July 2013, and we organized these results in tabular spreadsheets and compared them. We restricted the search to English-language articles that deal with unintentional overdose, focusing on 1 or more of the following key constructs: prevalence, time trends, mortality rates, and correlates. The term "overdose" as a MeSH major topic yielded 1076 publications. In addition, we searched the following combinations of nonmajor MeSH terms: "street drugs" and "overdose" yielded 180, "death" and "overdose" yielded 114, and "poisoning" and "drug users" yielded 17. There was some overlap among the searches. Based on the search and inclusion and exclusion criteria, we selected a total of 169 relevant articles for this article based on a close review of abstracts.

Results. We found wide variability in lifetime prevalence of experiencing a nonfatal overdose or witnessing an overdose, and in mortality rates attributable to overdose. Lifetime prevalence of witnessed overdose among drug users (n = 17 samples) ranged from 50% to 96%, with a mean of 73.3%, a median of 70%, and a standard deviation of 14.1%. Lifetime prevalence of drug users personally experiencing a nonfatal overdose (n = 27 samples), ranged from 16.6% to 68.0% with a mean of 45.4%, a median of 47%, and a standard deviation of 14.4%. Population-based crude overdose mortality rates (n = 28 samples) ranged from 0.04 to 46.6 per 100 000 person-years. This range is likely attributable to the diversity in regions, time periods, and samples. Most studies on longitudinal trends of overdose death rates or overdose-related hospitalization rates showed increases in overdose death rates and in overdose-related hospitalization rates across time, which have led to peaks in these rates at the present time. An overall trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across most of the literature. With the increase in prescription opioid overdose deaths, drug overdose is not just an urban problem: rural areas have seen an important increase in overdose deaths. Lastly, cocaine, prescription opioids, and heroin are the drugs most commonly associated with unintentional drug overdoses worldwide and the demographic and psychiatric correlates associated with unintentional drug overdoses are similar globally.

Conclusions. There is a need to invest in research to understand the distinct determinants of prescription drug overdose worldwide. Several other countries need to collect in a systematic and continuous fashion such data on sales of prescription opioids and other prescription drugs, nonmedical use of prescription drugs, and hospitalization secondary to overdoses on prescription drugs. The sparse evidence on the environmental determinants of overdose suggests a need for research that will inform the types of environmental interventions we can use to prevent drug overdose. Methodological issues for future studies include enhancing data collection methods on unintentional fatal and nonfatal overdoses, and collecting more detailed information on drug use history, source of drug use (for prescription drugs), and demographic and psychiatric history characteristics of the individual who overdosed. (*Am J Public Health.* 2015;105:e29–e49. doi:10.2105/AJPH.2015.302843)

PLAIN-LANGUAGE SUMMARY: Drug overdose is an important, yet inadequately understood, public health problem. The aim of this study was to systematically summarize the peer-reviewed literature to document the global epidemiological profile of unintentional drug overdoses, and the prevalence, time trends, mortality rates, and correlates of drug overdoses from 1980 until 2013. We found wide variability in prevalence mortality rates attributable to overdose. Most studies on longitudinal trends of overdose deaths or overdose-related hospitalizations showed increases across time. An overall trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across most of the literature. With the increase in prescription opioid overdose deaths, drug overdose is not just an urban problem: rural areas have seen an important increase in overdose deaths. Lastly, cocaine, prescription opioids, and heroin are the drugs most commonly associated with unintentional drug overdoses worldwide and the demographic and psychiatric correlates associated with unintentional drug overdoses are similar globally. Future studies need to collect more detailed information on drug use history, source of drug use (for prescription drugs), and demographic and psychiatric history characteristics of the individual who overdosed.

Worldwide attention to unintentional drug overdose has been limited by comparison with the scope of the problem.[1] There has been a substantial increase in drug overdose mortality in several countries worldwide over the past decade. The mortality rate from drug overdoses tripled in the United States between 1990 and 2006.[2] In the United States, unintentional overdose deaths among adults aged 25 to 64 years exceeded motor vehicle crash deaths and suicides as a leading cause of injury death from 2008 onward.[3] Likewise, unintentional overdose deaths outnumbered motor vehicle crash deaths in Australia in 2011.[4] In Europe, rates have been stable since 2005, but most European countries also have high overdose rates. For example, overdose rates of more than 20 deaths per million are found in 14 of 30 European countries, and rates of more than 40 deaths per million in 7 countries.[5]

Until recently, drug overdoses were seen as a substance abuse or law enforcement issue and not as a public health problem.[1] However, partly because of the increasing involvement of legal prescription drugs such as prescription opioids in drug overdoses, public health professionals have become more interested in the topic and in diminishing the societal burden posed by unintentional overdoses.[1]

Although drug overdose deaths attract much public attention,[1,6–8] there are substantial consequences of nonfatal overdose, including cardiac and muscular problems, cognitive impairment, renal failure, hearing loss, and injuries sustained during overdose.[9,10] Health care costs associated with overdose treatment are also substantial. From 1999 to 2008, hospitalization rates for overdoses in the United States increased by 55%, costing about $737 million in 2008.[11] There are little data available on drug overdose hospitalization costs in countries other than the United States.

Drug overdose can be defined as happening when

> someone . . . collapses, has blue skin, has convulsions, has difficulty breathing, loses consciousness, cannot be woken up, has a heart attack or dies while using drugs.[12(p704)]

This definition has been used widely across the literature.[13–16] Unintentional drug overdoses are unique among causes of morbidity and mortality in 2 respects. First, unintentional overdose deaths are rarely instantaneous and drug users rarely overdose alone. As such, for the most part, overdose deaths are avoidable deaths. For example, those who witness an overdose episode can call for help and apply first aid measures.[16] Opioid overdoses are preventable through the administration of naloxone, which can reverse the effect of opioids and can revive the individual.[16–18] Second, drug overdoses are inevitably and inextricably linked to the surrounding environment, particularly in the centrality of drug availability as a necessary (but insufficient) determinant of overdose.[19–23] Considering these observations that overdose is preventable and linked to surrounding environment, drug overdoses should be of concern to public health, both from the point of view of understanding their determinants and from the point of view of encouraging interventions to mitigate their consequences.

A systematic review of the drug overdose literature can help clarify what we know about unintentional drug overdoses and areas in which we have gaps in scholarship. Although reviews have been written about overdoses caused by particular types of drugs (e.g., prescription opioids, heroin, methadone),[24–27] in certain places (e.g., Utah),[28] on suicidal versus accidental overdose,[29] or on overdoses among recently released prisoners,[30] we are not aware of any global review of unintentional drug overdoses with the goal of synthesizing the prevalence, time trends, mortality rates, and correlates of drug overdose worldwide.

METHODS

The potential scope of literature that may be considered of interest to the topic is vast. We conducted a systematic review of publications available in the US National Library of Medicine's PubMed electronic database[31] in July 2013 by using different combinations of Medical Subject Headings (MeSH) search terms. We restricted the search to English-language articles published between 1980 and July 2013 that deal with unintentional overdose, focusing on 1 or more of the following key constructs: prevalence, time trends, mortality rates, and correlates. The term "overdose" as a MeSH Major Topic yielded 1076 publications. In addition, we searched the following combinations of nonmajor MeSH terms: "street drugs" and "overdose" yielded 180, "death" and "overdose" yielded 114, and "poisoning" and "drug users" yielded 17. There was some overlap among the searches. We did not use "unintentional" as a search term so as not to leave out studies that dealt with both intentional and accidental overdoses. There were no limitations in this original search on type of sample, or location or geography, but we excluded studies dealing with children, because, although this group is important, we aimed to focus only on studies that reported on unintentional drug overdoses among adults. We included commentaries because of their potential to shed light on potential interventions or trends. In addition, we reviewed reference lists of chosen articles to select additional studies or commentaries.

With these search and inclusion and exclusion criteria, we selected a total of 169 relevant articles for this study through a close review of abstracts (Figure 1). We were interested in articles that reported

1. population-based prevalence measures (46 articles; reported in Table 1),
2. studies that reported percentage of changes over time in trends of overdose (34 articles; Table 2),
3. mortality rates (53 articles; Table 3), and
4. correlates of overdose (summarized in the Results section, but not included in tables because of the lack of common quantitative measures to record these topics).

RESULTS

Table 1 shows prevalence of overdose found in relevant articles, organized by type of drug, sample, and type of prevalence (witnessed vs experienced, fatal vs nonfatal, and time point). Lifetime prevalence of witnessed overdose among drug users (n = 17 samples from 18 articles) ranged from 50% to 96%,[15–17,32,33,37,39,40,43–45,53,54,57–60,64] with a mean of 73.3%, a median of 70%, and a standard deviation of 14.1%. Although samples differed in demographics, length of drug use, and type of drug involved (e.g.,

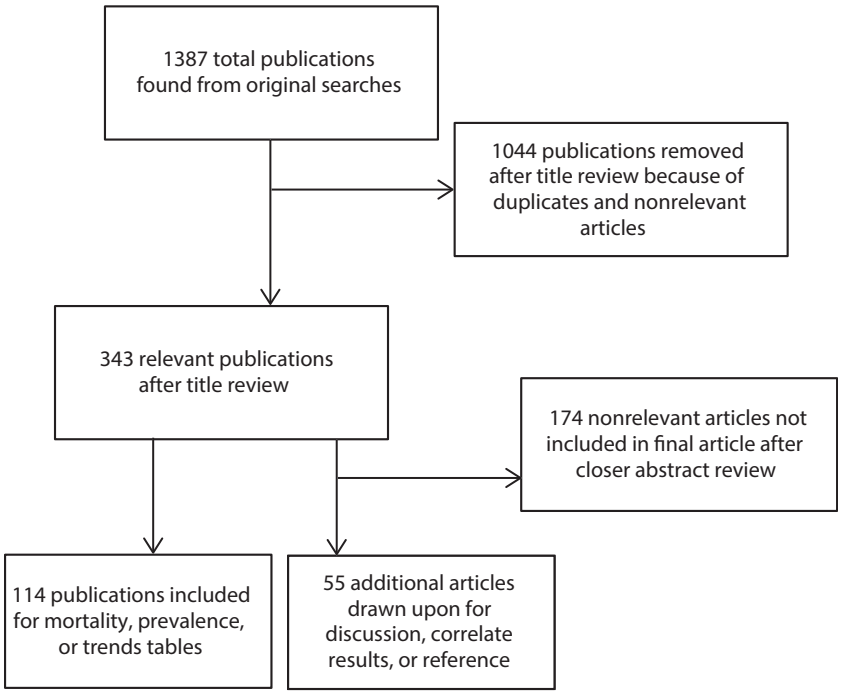

FIGURE 1—Flowchart of selection of peer-reviewed articles to document the worldwide epidemiological profile of unintentional drug overdoses.

prescription opioids, cocaine), the lifetime prevalence of witnessing an overdose did not differ greatly between studies conducted in different settings and countries.

Two studies reported lifetime prevalence of witnessing a fatal overdose specifically: 1 found that 4 of 24 drug users attending a general medical practice in inner-city Dublin, Ireland, in 1998 to 1999 had witnessed a fatal overdose[40]; the other reported a 15% prevalence among 763 injection drug users from 16 different cities of the Russian Federation.[59] Two studies reported past-year prevalence of witnessed fatal or nonfatal overdose: 50% among 973 users aged younger than 30 years who had injected drugs in the previous month in 4 neighborhoods of San Francisco, California,[58] and 58% of 212 users in Dorset, United Kingdom, who had injected in the previous 2 months.[62] One study of drug users aged 18 years or older in New York City (n = 1184) reported past-6-month prevalence of witnessing overdose at 35.2%[16] and 2 samples of injection drug users reported past-3-month prevalence of witnessing overdose at 48.5% and 50%.[32,55]

Lifetime prevalence of drug users personally experiencing a nonfatal overdose had a considerably wider range across studies (n = 29 samples), varying from 16.6% to 68.0%,[9,13–16,32,37–44,46–48,50,53,56,58–61,63,64,67–69] with a mean of 45.4%, a median of 47%, and a standard deviation of 14.4%. Past-year prevalence of drug users personally experiencing a nonfatal overdose (n = 14 samples) ranged from 4.0% to 38.0%,[9,35,36,42,46–50,52,58,62,63,67] with a mean of 18.8%, a median of 16.8%, and a standard deviation of 8.9%. Past-6-month prevalence of drug users personally experiencing a nonfatal overdose ranged from 6.7% to 33% (n = 7 samples),[19,34,51,61,65,66,70] with a mean of 18.5%, a median of 17%, and a standard deviation of 10.4%. Two studies reported past-3-month prevalence of overdose: one found that 11.9% of drug users had overdosed out of 644 users younger than 30 years in San Francisco who had injected in the past 30 days[56] and the other found a prevalence of 15.2% among injection drug users, most of whom were homeless or in temporary housing, in Los Angeles, California, in 2006.[55]

Trends

We reviewed articles for overall longitudinal trends of overdose death rates or overdose-related hospitalization rates (Table 2). Rates of increase for overdose deaths in population samples caused by any substance ranged from a 5.3% average increase per year in the United States from 1979 to 1990 to a 400% increase in both Glasgow, Scotland, between 1991 and 1992, and Vermont between 2001 and 2006.[6,71–73,75–85]

Between 1974 and 1992 in England and Wales, there was a 1186% increase in lethal self-poisonings from heroin alone.[101] In the same location between 2007 and 2008, there was an 8% increase in heroin or morphine deaths among women, and a 20% increase in cocaine deaths among women.[85] There was a 21.4% decrease in illicit drug overdose deaths in Florida between 2003 and 2009,[82] and a 43% to 85% decrease among all drug-related deaths in Australia in 2001.[74] In the Australian study, the reduction is believed to have been driven mainly by a reduction in heroin supply. A 34% decrease in illicit drug overdose deaths was seen in the city of Chicago, Illinois, from 2000 to 2003.[95] One study reported a 55% increase in hospitalization rates for drug overdoses on all substances among a nationwide sample in the United States from 1999 to 2008.[11]

An overall trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across most of the literature.[80–82,89,90,96,97,99,100] With the exception of Australia, which experienced a 60% decrease in opioid deaths between 1990 and 2001,[91] most studies in Table 2 reported increased rates of deaths from opioids.2,[6,80–82,87,90,92,100] For example, there was a 467.7% increase reported in methadone

TABLE 1—Studies Reporting the Prevalence of Unintentional Drug Overdose Worldwide, 1980–2013

Reference	Type of Drug[a]	Location and Time Period	Sample or Source	Type of Prevalence	Time Point	Prevalence, %
Coffin et al.[15]	All substances	New York, NY, 2001–2004	Street-recruited habitual drug users[b] (n = 772)	Witnessed, both fatal and nonfatal	Lifetime	68.5
				Experienced (nonfatal)	Lifetime	16.6
Galea et al.[32]	All substances	New York, NY, 2004–2005	Overdose prevention and reversal program through a syringe exchange program—pilot study (n = 25)	Experienced (nonfatal)	Lifetime	68.0
				Witnessed, both fatal and nonfatal		83.0
					Past 3 mo (of follow-up)	50.0
Tobin et al.[33]	All substances	Baltimore, MD, 2002–2003	Self-Help in Eliminating Life-Threatening Diseases HIV-prevention study[c]	Witnessed, both fatal and nonfatal	Lifetime	70.0
Werb et al.[34]	All substances	Vancouver, BC, 2005–2006	At-Risk Youth Study (n = 478)	Experienced (nonfatal)	Past 6 mo	11.0
Britton et al.[35]	All substances (treatment sample)	11 mid- to large urban areas in the United States	Drug Abuse Treatment Outcomes Study[d]	Experienced (nonfatal)	Past year (after treatment)	3.1
Tracy et al.[16]; Bohnert et al.[17]	Heroin, crack, and cocaine	Central Harlem and South Bronx, NY, 2001–2004	Targeted street outreach of drug users aged ≥ 18 y (n = 1184)	Witnessed, both fatal and nonfatal	Lifetime	67.3
				Witnessed, both fatal and nonfatal	Past 6 mo	35.2
			Among those who had ever witnessed (n = 672)	Experienced (nonfatal)	Lifetime	45.0
Bohnert et al.[14]	Heroin, crack, and cocaine	Central Harlem and South Bronx, NY, 2001–2004	Analytic sample = 1093	Experienced (nonfatal)	Lifetime	37.5
Galea et al.[36]	Heroin, crack, and cocaine	Central Harlem and South Bronx, NY, 2001–2004	Among 928 persons who used cocaine during the past year	Experienced (nonfatal)	Past year	17.0
	Heroin, crack, and cocaine		Among 1059 persons who used heroin during the past year			16.8
Lagu et al.[37]	Heroin and cocaine	Providence, RI, 2002–2004	329 study participants[e]	Witnessed, both fatal and nonfatal	Lifetime	64.6
				Experienced (nonfatal)		34.6
Brådvik et al.[38]	Heroin	Malmö, Sweden, 2003	149 regular heroin users	Experienced (nonfatal)	Lifetime	65.8
Baca and Grant[39]	Heroin	Albuquerque, NM, 2002	Recruited from a syringe-exchange program: aged ≥ 18 y, used heroin in past 3 mo (n = 101)	Witnessed, both fatal and nonfatal	Lifetime	94.1
				Experienced (nonfatal)	Lifetime	64.4
Cullen et al.[40]	Heroin	Dublin, Ireland, 1998–1999	Questionnaire-based interview of drug users attending an inner city general practice (n = 24)	Witnessed, both fatal and nonfatal	Lifetime	96.0
			Questionnaire-based interview	Witnessed fatal		17.0
			Questionnaire-based interview	Experienced (nonfatal)		42.0
Darke et al.[41]	Heroin	Sydney, Australia, 2001–2002	ATOS cohort of 615 heroin users[f]	Experienced (nonfatal)	Lifetime	54.0

Continued

TABLE 1—*Continued*

Darke et al.[42]	Heroin	Southwestern Sydney, Australia, 1995–1996	112 heroin users recruited through needle and syringe exchanges; had used heroin in preceding 24 hr	Experienced (nonfatal)	Lifetime	53.0
					Past year	16.4
Kerr et al.[43]; Kerr et al.[44]	Heroin	Melbourne, Australia, 2007	99 injecting heroin users were recruited and interviewed at needle and syringe programs	Witnessed, both fatal and nonfatal	Lifetime	84.0
				Experienced (nonfatal)	Lifetime	61.0
Darke et al.[9]	Heroin	New South Wales, Australia, 2001–2005	Cohort study of 387 heroin users: ATOS	Experienced (nonfatal)	Lifetime (at baseline)	55.0
					Past year (at baseline)	26.6
					Past 3 y (of follow-up)	18.6
Darke et al.[45]	Heroin	Sydney, Australia, 1994	329 heroin users	Witnessed, both fatal and nonfatal	Lifetime	86.0
Darke et al.[46]	Heroin	Sydney, Australia, 1994	329 heroin users	Experienced (nonfatal)	Lifetime	68.0
					Past year	29.0
Gossop et al.[47]	Heroin	South London, UK, 1992–1994	Drug Transitions Project: 438 heroin users were contacted and interviewed by privileged-access interviewers	Experienced (nonfatal)	Lifetime	23.0
					Past year	9.4
Seal et al.[48]	Heroin or “speedballs” (a cocaine and heroin mixture)	San Francisco, CA, 1998–1999	1427 heroin injectors were recruited from 6 inner-city neighborhoods (part of UHS)	Experienced (nonfatal)	Lifetime	48.0
					Past year	13.0
Taylor et al.[49]	Injected heroin only	Glasgow, Scotland, 1993–1994	1018 recruited IDUs	Experienced (nonfatal)	Past year	22.0
	Injected heroin + other drugs					32.0
	Methadone					29.0
	Buprenorphine					26.0
	Temazepam					31.0
	Cocaine					37.0
	Ecstasy					38.0
Bluthenthal et al.[50]	Injection drugs	San Francisco, CA, 1997	UHS: 1114 street-recruited, active IDUs in 6 San Francisco Bay Area communities	Experienced (nonfatal)	Lifetime	42.0
			UHS: 1114 street-recruited, active IDUs in 6 San Francisco Bay Area communities	Experienced (nonfatal)	Past year	12.3
Seal et al.[51]	Injection drugs	San Francisco, CA, 2001	UHS (n = 487): recruited from street settings in San Francisco and screened for enrollment[g]	Experienced (nonfatal)	Past 6 mo (baseline)	17.0

Continued

TABLE 1—*Continued*

		San Francisco, CA, 2002			Past 6 mo (follow-up)	12.0
Jenkins et al.[52]	Injection drugs (primarily heroin)	Seattle, WA, 2009	Seattle and King County[h] (n = 447 clients)	Experienced (nonfatal)	Past year	16.0
Sherman et al.[53]	Injection drugs	Baltimore, MD, 1999–2002	Risk Evaluation and Assessment of Community Health III[i] (n = 309)	Witnessed, both fatal and nonfatal	Lifetime	57.0
				Experienced (nonfatal)		29.0
Pollini et al.[54]	Injection drugs	Baltimore, MD, 2003–2004	Cross-sectional survey administered to 924 IDUs in ongoing cohort study	Witnessed, both fatal and nonfatal	Lifetime	69.7
Wagner et al.[55]	Injection drugs	Los Angeles, CA, 2006	HRC[j] (n = 66)	Experienced (nonfatal)	Past 3 mo (at baseline)	15.2
				Witnessed, both fatal and nonfatal		48.5
Evans et al.[56]	Injection drugs	San Francisco, CA, 1997	UFO ("U Find Out") Study[k] (n = 644)	Experienced (nonfatal)	Lifetime	39.1
				Experienced (nonfatal)	Past 3 mo (at baseline)	11.9
Seal et al.[57]	Injection drugs	San Francisco, CA, 1999–2000	UHS[l] (n = 82)	Witnessed, both fatal and nonfatal	Lifetime	89.0
Davidson et al.[58]	Injection drugs	San Francisco, CA, 1997–2000	IDUs aged < 30 y[m] (n = 973)	Witnessed, both fatal and nonfatal	Lifetime	73.0
					Past year	50.0
				Experienced (nonfatal)	Lifetime	47.0
					Past year	26.8
Ochoa et al.[13]	Injection drugs	San Francisco, CA, 1996	Drug users aged 14–29 y[n]	Experienced (nonfatal)	Lifetime	48.0
Sergeev et al.[59]	Injection drugs	Russian Federation, 2001	Harm Reduction Training Project[o] (n = 763)	Witnessed, both fatal and nonfatal	Lifetime	81.0
				Witnessed fatal		15.0
				Experienced (nonfatal)		59.0
Powis et al.[60]	Injection drugs	London, UK, 1994–1995	312 current IDUs[p]	Witnessed, both fatal and nonfatal	Lifetime	54.0
				Experienced (nonfatal)		38.0
Fairbairn et al.[19]	Injection drugs	Vancouver, BC, 2003–2005	Vancouver Injection Drug Users Study (n = 551)	Experienced (nonfatal)	Past 6 mo (follow-up)	6.7
Kerr et al.[61]	Injection drugs	Vancouver, BC, 1996–2004	Vancouver Injection Drug Users Study[q] (n = 1587)	Experienced (nonfatal)	Lifetime (at baseline)	47.0
					Past 6 mo (follow-up)	32.7
Bennett and Higgins[62]	Injection drugs	Dorset, UK, 1995–1996	Drug users who had injected in the 2 mo before interview (n = 212); multisource sampling	Experienced (nonfatal)	Past year	30.0
				Witnessed, both fatal and nonfatal		58.0
Bergenstorm et al.[63]	Opioids	Bac Ninh and Tu Son, Vietnam, 2003	299 out-of-treatment male opioid IDUs aged 18–45 y; community-based cross-sectional survey	Experienced (nonfatal)	Lifetime	43.5
					Past year	36.1
Havens et al.[64]	Prescription opioids, cocaine, heroin, and methamphetamine	Rural Appalachian Kentucky, year undisclosed	Social Networks Among Appalachian People Study[r] (n = 400)	Witnessed, both fatal and nonfatal	Lifetime	58.2
				Experienced (nonfatal)		28.0

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TABLE 1—*Continued*

Fischer et al.[65]; Fischer et al.[66]	Illicit opioids	Vancouver, BC, Edmonton, AB, Toronto, ON, Montréal, QC, and Québec, QC, 2002	The Interdisciplinary Health Research Team on Illicit Opiate Addiction Research, Treatment, and Policy[s] (n = 651)	Experienced (nonfatal)	Past 6 mo	17.2
Tobin et al.[67]	Cocaine and opioids	Baltimore, MD, 2000	729 opioid and cocaine users completed a cross-sectional survey	Experienced (nonfatal)	Lifetime	35.0
					Past year	4.0
Man et al.[68]	Opioids (methadone + diazepam)	Southern England, and Glasgow and Edinburgh, Scotland, 1999–2000	Opioid users interviewed in 4 drug misuse treatment services (n = 135)	Experienced (nonfatal)	Lifetime	56.0
Silva et al.[69]	Prescription opioids and tranquilizers	New York, NY, and Los Angeles, CA, 2009–2011	596 participants aged 16–25 y[t]	Experienced (nonfatal)	Lifetime	23.6
Kinner et al.[70]	Illicit drugs	Vancouver, BC, 1996–2010	Prospective cohort of 2515 community-recruited illicit drug users	Experienced (nonfatal)	Past 6 mo	33.0

Note. ATOS = Australian Treatment Outcome Study; HRC = Homeless Health Care Los Angeles Center for Harm Reduction; IDUs = injection drug users; UHS = Urban Health Study.

[a]All substances = opioid and nonopioid substances, both pharmaceutical and illicit, including alcohol.

[b]Participants were users who had been injecting for at least 1 year, had injected heroin within the past 2 months, and were aged ≥ 18 years.

[c]Snapshot of fourth wave (n = 568); recruited through street-based outreach, advertisements, and word of mouth; inclusion criteria were aged ≥ 18 years, having daily contact with drug users, and willingness to conduct HIV prevention outreach.

[d]A longitudinal naturalistic multisite study; participants included 2966 patients with ≥ 1 substance abuse disorders.

[e]Participants were recruited for a health service research study on drug users if they (1) were aged 18–70 years; (2) had injected heroin or cocaine during the preceding 30 days, or noninjection heroin or cocaine use at least weekly for the past 6 months; (3) had < 30 of the last 90 days spent in institutional settings including prisons and residential drug treatments or hospitalization; (4) spoke English; (5) denied intent to harm self or others; and (6) had absence of psychosis.

[f]The cohort consisted of entrants to treatment of heroin dependence in opioid maintenance, detoxification, and residential rehabilitation; in addition, a group of heroin users not currently in treatment were recruited from needle and syringe programs in the regional health areas from which treatment entrants were recruited.

[g]Eligible if they injected heroin > 2 times/wk, reported ≥ 1 heroin overdoses in the past 5 year, and could enroll together with an eligible injection partner who met the same criteria.

[h]Sites included 2 indoor and 2 outdoor exchanges in Seattle, as well as a mobile exchange in suburban King County; n = 447 clients who reported opioid use since the beginning of the year (between January 2009 and the date the survey was administered in April or May of 2009).

[i]Longitudinal study of 309 15- to 30-year-old IDUs and non-IDUs who had initiated heroin, cocaine, or crack use within 5 y before study enrollment.

[j]IDUs, most of whom were homeless or in temporary housing, aged ≥ 18 y; participants were recruited via street outreach, distribution of advertising leaflets, and 1-on-1 recruitment within the HRC.

[k]IDUs aged < 30 years, recruited by peer outreach workers with study invitation cards and flyers, contacts with youth-friendly neighborhood groups and community providers, and word of mouth; had to have self-reported use of injection drugs in the past 30 days.

[l]Outreach and word of mouth using targeted sampling methods; eligibility determined by physical evidence of recent injection drug use ("tracks" or multiple venipuncture sites) or participation in previous cross-sections of data collection (final n = 82 who had experienced an overdose and wanted to participate, out of original 552).

[m]IDUs aged < 30 years who had injected in the previous month in 4 neighborhoods of San Francisco; outreach and word of mouth.

[n]Drug users aged 14–29 years who had injected drugs in the previous 6 months; study participants were recruited and interviewed at 6 needle exchanges and 3 youth outreach sites.

[o]763 IDUs from 16 cities of the Russian Federation as part of the Harm Reduction Training Project.

[p]312 current IDUs were recruited and interviewed in community settings by a team of privileged-access interviewers.

[q]Persons were eligible if they had injected illicit drugs at least once in the previous month and resided in the greater Vancouver region.

[r]Users aged ≥ 18 years, residing in an Appalachian county in Kentucky, and had used ≥ 1 of the following drugs to get high in the previous 30 days: prescription opioids, cocaine, heroin, or methamphetamine.

[s]Participants were recruited by a variety of methods, including dissemination of flyers at user contact points such as needle exchanges, advertisements in community articles, and snowball sampling.

[t]Interviewed a sample of 596 16- to 25-year-old patients in Los Angeles and New York who had engaged in misuse of a prescription drug (i.e., opioid, tranquilizer, stimulant, or any combination) ≥ 3 times in the past 90 days.

TABLE 2—Studies Reporting Trends Across Time in Unintentional Overdose Worldwide, 1980–2013

Reference	Type of Drug[a]	Location and Time Period	Sample or Source	Measure	Trend or Change
CDC[71]	All substances	United States, 1990–2001	CDC, National Center for Injury Prevention and Control	Overdose death rate	56% increase
		11 US states,[b] 1990–2001			145% average increase (range = 28%–325% [FL = 325%])
White et al.[11]	All substances	United States, 1999–2008	Nationwide inpatient sample[c]	Hospitalization rates	55% increase
Paulozzi et al.[72]	All substances	United States, 1990–2003	National Center for Health Statistics: Whites	Drug-induced death rate	189% increase
			National Center for Health Statistics: African Americans		64% increase
Paulozzi et al.[73]	All substances	United States, 1999–2004	NVSS	Unintentional and undetermined drug poisoning mortality rates	62.0% increase
			NVSS, metropolitan counties only		51.0% increase
			NVSS, nonmetropolitan counties only		159% increase
Degenhardt et al.[74]	All substances	New South Wales, Australia, 2001	Multiple[d]	Drug-related deaths that appeared to be driven by the reduction in heroin supply	43% decrease
		Victoria, Australia, 2001			85% decrease
Edwards et al.[75]	All substances	Vermont, 2006–2009	Medical Examiner's Office	Drug-induced death rate	27.4% increase
		Vermont, 2009–2010			16.0% decrease
Wunsch et al.[76]	All substances	Western Virginia, 1997–2003	Retrospective, population-based review of medical examiner cases	Deaths with a direct or contributing cause of drugs	300% increase
Hammersley et al.[77]	All substances	Glasgow, Scotland, 1991–1992	The Department of Forensic Medicine and Science Laboratory	Drug-induced death rate	400% increase
Shah et al.[78]; Mueller et al.[79]	All substances	New Mexico, 1990–2005	New Mexico Office of the Medical Investigator	Unintentional drug overdose death numbers and rates	176.8% increase
Paulozzi et al.[80]	All substances	United States, 1979–1990	NCHS	Unintentional drug poisoning mortality rates	5.3% increase (average per year)
		United States, 1990–2002			18.1% increase (average per year); 217.6% total
	Opioid analgesics without heroin and cocaine	United States, 1999–2002		Number of poisonings on death certificates	129.2% increase
	Heroin				12.4% increase
	Cocaine				22.8% increase
Fingerhut et al.[81]	All substances	United States, 1999–2005	NVSS	Number of poisoning deaths	65.6% increase
	Methadone				467.7% increase
	Heroin				2.4% increase
	Other opioids				110% increase
	Cocaine				62.5% increase
	Cannabis				202.7% increase

Continued

TABLE 2—*Continued*

CDC[82]	All substances	Florida, 2003–2009	Florida Medical Examiners Commission	Overdose death rate	47.5% increase
	Prescription drugs				84.2% increase
	Illicit drugs				21.4% decrease
Madden and Shapiro[83]	All substances	Vermont, 2001–2006	Retrospective review of the Vermont Office of the Chief Medical Examiner	Overdose deaths	400% increase
	Methadone			Proportion of overall deaths that include methadone	300% increase
Socie et al.[84]	All substances	United States, 1996–2006	CDC WISQARS Fatal Injury Reports" (WISQARS = Web-Based Injury Statistics Query and Reporting System)	Poisoning death rate	74% increase
		Ohio, 1996–2006			178% increase
		Ohio, 1999–2008			325% increase
Wells et al.[85]	All substances	England and Wales, 2007–2008	National Statistics database	Drug poisoning deaths, men	8% increase
				Drug poisoning deaths, women	17% increase
	Heroin and morphine			Drug poisoning deaths, women	8% increase
	Cocaine			Drug poisoning deaths, women	20% increase
CDC[6]	All substances	United States, 1999–2010	CDC	Drug poisoning deaths, women	151% increase
				Drug poisoning deaths, men	85% increase
	Opioids			Drug poisoning deaths, women	500% increase
Wisniewksi et al.[86]	Oxycodone	United States, 1995–2002	Consolidated from the Drug Abuse Warning Network database[e]	Emergency department visits	560% increase
	Morphine				116% increase
	Hydrocodone				160% increase
Cerdà et al.[2]	Prescription analgesics	New York, NY, 1990–2006	Office of the Chief Medical Examiner of NYC	Overdose death rate	700% increase
CDC[87]	Methadone	United States, 1999–2009	NVSS	Overdose death rate	550% increase
Hawton et al.[88]	Coproxamol	England and Wales, 1998–2010	Office for National Statistics	Number of overdose deaths after withdrawal of coproxamol	62% decrease (after intervention)
The DAWN Report[89]	Prescription drugs	United States, 2004–2011	Drug Abuse Warning Network database	Emergency department visits	232.5% increase
Green et al.[90]	Opioids	Connecticut, 1997–2007	Connecticut Office of the Chief Medical Examiner	Absolute number of overdose deaths	44% increase
				Overdose deaths with toxicological data	80% increase
	Methadone			Overdose deaths	379% increase
Degenhardt et al.[91]	Opiods	New South Wales, Australia, 1999–2001	Australian Bureau of Statistics, et al.[f]	Opioid deaths	60% decrease
		2000–2002		Presentations of opioid overdose to emergency departments	45% decrease
Calcaterra et al.[92]	Pharmaceutical opioids	United States, 1999–2009	CDC WONDER Database; 15- to 64-year-old patients	Age-adjusted death rate	292.9% increase

Continued

TABLE 2—*Continued*

Cochella et al.[93]; Johnson et al.[94]	Prescription opioids	Utah, 2007–2008	Intervention[g]	Medication-related overdose deaths following program implementation	14.0% decrease (after intervention)
Scott et al.[95]	Illicit opioids	Chicago, IL, 2000–2003	Death certificates[h]	Incidence of fatal overdose	34% decrease
Marshall et al.[96]; Wood et al.[97]	Injection drugs	Vancouver, BC, 2001–2005	British Columbia Coroners Service	Overdose death rates after opening of first medically supervised safe-injection facility	35% decrease (after intervention)
Friedman[98]	Heroin and fentanyl	Illinois, 2006–2005	Poison Control data	Heroin-related calls	63.6% increase
Schwartz et al.[99]	Heroin	Baltimore, MD, 1995–2002 vs 2003–2009	Baltimore City Health Department	Average annual heroin overdose deaths (after buprenorphine became available)	37% decrease
Maxwell et al.[100]	Heroin	Chicago, IL, 1996–2000	The Chicago Recovery Alliance, The Medical Examiner of Cook County	Opioid overdose deaths	400% increase
		Chicago, IL, 2000–2001		After prevention program started providing naloxone	20% decrease (after intervention)
Neeleman and Farrell[101]	Heroin alone	England and Wales, 1974–1992	Office of Population Censuses and Surveys tabulations	Lethal self-poisonings (including accidental, suicidal, and unknown)	1186% increase
	Methadone with or without heroin		Office of Population Censuses		823% increase

Note. CDC = Centers for Disease Control and Prevention; NCHS = National Center for Health Statistics; NVSS = National Vital Statistics System; NYC = New York City; WONDER = Wide-Ranging Online Data for Epidemiologic Research.

[a]All substances = opioid and nonopioid substances, both pharmaceutical and illicit, including alcohol.

[b]Colorado, Delaware, Kentucky, New Mexico, Florida, Massachusetts, North Carolina, Oregon, Washington, Utah, Wisconsin.

[c]Designed to approximate a 20% sample of US community hospitals as defined by the American Hospital Association. Poisoning and nondependent abuse of alcohol and drugs in patients aged 18–24 years.

[d]Hospital emergency departments, ambulance services, and coroner's systems; treatment entries for heroin dependence compiled by state health departments; numbers of needles and syringes distributed to drug users; and data on arrests for heroin-related incidents and property-related crime incidents compiled by State Police Services.

[e]Medical record and toxicology screening data from a nationally representative hospital sample.

[f]Australian Bureau of Statistics and the Division of Analytical Laboratories, Institute of Clinical Pathology and Medical Research, Western Sydney Area Health Service, the Ambulance Service of New South Wales Case Sheet Database, and other emergency department data.

[g]"Presentations highlighting six recommended prescribing practices were developed and presented to health care workers. Participants were encouraged to utilize the state prescription database and to complete a series of surveys assessing confidence and behavior changes at 0, 1, and 6 months post-presentation. Continuing medical education credits incentivized participation."[93(pS73)]

[h]Manually screened death certificates from the Illinois Department of Public Health master death files, 1999–2003, and the Chicago Real Time Death Surveillance System, 2003.

deaths in the United States between 1999 and 2005,[81] and a 129.2% increase in deaths from prescription opioids, between 1999 and 2002.[80]

Mortality Rates

Relevant studies that reported either population-based mortality rates attributable to fatal drug overdose, or all-cause and cause-specific death rates among drug users, are presented in Table 3, organized by type of drug, location and time period, and sample. Rates are crude and overdose-related, unless otherwise noted in the table. Rates are reported as number of deaths per 100 000 person-years; we converted original rates from articles that were presented on a different scale accordingly. Mortality rates differed widely depending on the setting and on the source population (i.e., any substance users, injection drug users only, recently released prisoners).

Population-based crude overdose mortality rates (n = 30 samples from 22 articles) ranged from 0.04 to 46.6 per 100 000 person-years.[5,7,22,41,71,73,76,81,82,84,92,95,107,109–111,121–123,125–127] This range is likely attributable to the diversity in regions, time periods, and samples. The highest rates were generally seen in cities such as Barcelona, Spain,[111] and Chicago among high-poverty communities,[95] or in very rural areas such as West Virginia[125] and Wilkes County, North Carolina,[127] the latter of which was before an intervention. Population-based adjusted or standardized rates (n = 35 samples from 12 articles) ranged from 0.11 to 253.8,[2,78,79,92,96,102,103,105,108,111,132,134] the highest rate being that of Vancouver, British Columbia, before the opening of the first medically supervised safe injection facility.[96]

TABLE 3—Studies Reporting Mortality Rates of Unintentional Drug Overdoses Worldwide, 1980–2013

Reference	Type of Drug[a]	Location and Time Period	Sample or Source	Mortality Rate per 100 000 Person-Years, Crude Unless Noted
Duncan[102]	All substances	United States, 1981	Division of Vital Statistics et al.[b]	3.1 (age-adjusted)
		United States, 1982		3.1 (age-adjusted)
		United States, 1983		3.1 (age-adjusted)
		United States, 1984		3.2 (age-adjusted)
		United States, 1985		3.5 (age-adjusted)
		United States, 1986		4.0 (age-adjusted)
		United States, 1987		3.8 (age-adjusted)
		United States, 1988		4.2 (age-adjusted)
		United States, 1989		4.1 (age-adjusted)
		United States, 1990		3.6 (age-adjusted)
		United States, 1991		3.8 (age-adjusted)
CDC[71]	All substances	United States, 2001	CDC, National Center for Injury Prevention and Control	7.8
Paulozzi et al.[73]	All substances	United States, 2004	NVSS	7.8
Warner et al.[103]	All substances	United States, 2008	NVSS	9.2 (age-adjusted)
CDC[6]	All substances	United States, 2010	CDC; female rate	9.8
Merrall et al.[104]	All substances	Scotland, 1996–2000	Scottish Drug Misuse Database cohort[c]	498 (95% CI = 454, 545)
		Scotland, 2001–2005		357 (95% CI = 334, 381)
Shah et al.[78]; Mueller et al.[79]	All substances	New Mexico, 1990–2005	New Mexico Office of the Medical Investigator	10.4 (age-adjusted)
Shah et al.[105]	All substances	New Mexico, 2005–2009	New Mexico Office of the Medical Investigator	17.6 (95% CI = 16.8, 18.5; age-adjusted)
Socie et al.[84]	All substances	Ohio, 2008	CDC WISQARS Fatal Injury Reports; Ohio Department of Vital Statistics	13.7
Wunsch et al.[76]	All substances	Metropolitan Virginia, 1997–2003	Office of the Medical Examiner[d]	6.77 (95% CI = 6.12, 7.42)
		Micropolitan Virginia, 1997–2003		7.68 (95% CI = 6.16, 9.20)
		Rural Virginia, 1997–2003		10.76 (95% CI = 9.67, 11.85)
Farrell and Marsden[106]	All substances	England and Wales, 1998–2003	National sample of prisoners[e]: men	520 (converted)
			National sample of prisoners[e]: women	590 (converted)
EMCDDA[5]	All substances	European Union, 2010	EMCDDA; population aged 15–64 y	2 (converted)
Marshall et al.[107]	Illicit drugs	British Columbia, 2001–2005	British Columbia Coroners Service[f]	4.38 (95% CI = 4.10, 4.67)
	Cocaine			2.58
Milloy et al.[108]	Illicit drugs	British Columbia, 2001–2005	British Columbia Coroners Service	4.84 (age-adjusted)
			Among those with First Nations identity	13.3 (age-adjusted)
Harlow[109]	Narcotics (heroin, morphine, dilaudid, etc.)	Texas, 1976–1987	Medical examiner or death certificates filed with the Texas Department of Health	0.13–0.92
	Cocaine	Texas, 1983–1987		0.04–0.09

Continued

TABLE 3—*Continued*

Galea et al.[22]; Coffin et al.[110]	Cocaine, opioids, alcohol	New York, NY, 1990–1998	Office of the Chief Medical Examiner of NYC[g]	7.3–13.3
Torralba et al.[111]	Cocaine and opioids	Barcelona, Spain, 1989–1993	City residents in the age group 15–49 y; used the Forensic Institute, and the Sistema d'Informacio de Drogues de Barcelona	15.3 (95% CI = 14.1, 16.5; age- and sex-adjusted)
Marzuk et al.[112]	Cocaine and opioids	New York, NY, 1990–1992	Office of the Chief Medical Examiner of NYC and Census data	1.27 (Upper East Side; age-adjusted); 38.76 (Central Harlem; age-adjusted)
Tardiff[113]	Cocaine without opioids	New York, NY, 1990–1992	Office of the Chief Medical Examiner of NYC and Census data	2.86
	Opioids without cocaine			2.29
	Cocaine and opioids			3.42
Cerdà et al.[2]	Cocaine	New York, NY, 1993–1995	Office of the Chief Medical Examiner of NYC	15.5 (age-adjusted)
	Heroin			14.1 (age-adjusted)
	Prescription analgesics	New York, NY, 2006		2.7 (age-adjusted)
	Methadone			4.4 (age-adjusted)
Stenbacka et al.[114]	Illicit drugs	Stockholm, Sweden, 1967–2003	Users with substance abuse problems (n = 1705)[h]	277 (95% CI = 258, 295; converted; all-cause)
Evans et al.[56]	Injection drugs	San Francisco, CA, 1997–2007	UFO ("U Find Out") Study[i]	912 (95% CI = 663, 1253; converted; all-cause)
Vlahov et al.[115]	Injection drugs	5 US cities,[j] 1997–2002	Collaborative Injection Drug Users Study[j]	7.1
Marshall et al.[96]	Injection drugs	Vancouver, Canada, 2001–2003	British Columbia Coroners Service	253.8 (95% CI = 187.3, 320.3; standardized)
		2003–2005		165.1 (108.8, 221.4; standardized)
Hickman et al.[116]	Injection drugs	Bristol, England, 2005–2006	Respondent driven sampling and local Office for National Statistics mortality files; among drug users	400 (converted)
Manfredi et al.[117]	Injection drugs	Bologna, Northeastern Italy, 1977–2002	Open cohort of 1214 IDUs, mostly heroin addicts, referring to a specialized outpatient center	451.8 (converted)
Miller et al.[118]	Injection drugs	Vancouver, BC, 1996–2004	Vancouver Injection Drug User Study[k]	1368 (all-cause)
Wang et al.[119]	Injection drugs	Baltimore, MD, 1988–2001	ALIVE cohort study: 1927 actively IDUs HIV seronegative at baseline (308 later HIV seroconverted)	1390 (converted)
			ALIVE cohort study, but among seronegative drug users	560 (converted)
Brettle et al.[120]	Injection drugs	Edinburgh, Scotland, 1986–1994	HIV-positive patients from the Edinburgh City Hospital cohort records	1120 (converted)

Continued

TABLE 3—*Continued*

Calcaterra et al.[92]	Heroin	United States, 2007	CDC WONDER Database; 15- to 64-year-old individuals	1.05 (95% CI = 1.00, 1.09)
		United States, 2009		1.43 (95% CI = 1.38, 1.48)
Darke et al.[41]	Heroin	Sydney, Australia, 2001–2009	Australian Treatment Outcome Study cohort of 615 heroin users[l]	643 (95% CI = 437, 913; converted)
Davidson et al.[121]	Heroin	San Francisco, CA, 1997–2000	Medical examiner's case files, Census data	14.29
Ruttenber and Luke[122]	Heroin	District of Columbia, 1981	Deaths associated with injected street preparations of heroin (population-based)	17.4
Calcaterra et al.[92]	Pharmaceutical opioids	United States, 1999	CDC WONDER Database; 15- to 64-year-old patients	1.54 (95% CI = 1.49, 1.60; age-adjusted)
		United States, 2009		6.05 (95% CI = 5.95, 6.16; age-adjusted)
CDC[7]	Opioid painkillers	Washington State, 2006	CDC; health and human services agencies in WA	6.4
			CDC; health and human services agencies in WA, but among only Medicaid-enrolled population	30.8 (age-adjusted)
Fingerhut et al.[81]	Methadone	United States, 2005	NVSS	1.5
CDC[87]	Methadone	United States, 2007	NVSS	1.8
CDC[123]	Methadone	United States, 2009	NVSS	1.5
Soyka et al.[124]	Methadone and buprenorphine	Munich, Germany	2694 opioid-dependent patients in substitution treatment through the COBRA study	1040 (converted; all-cause)
CDC[82]	All substances	Florida, 2009	Florida Medical Examiners Commission	15.7
	Prescription drugs			13.4
	Illicit drugs			3.4
Hall et al.[125]	Prescription drugs	West Virginia, 2006	Population-based, observational study[m]	16.2
Niveau et al.[126]	Opioids	Geneva, Switzerland, 1999	Cantonal Office of Statistics	3.19
Albert et al.[127]	Opioids	Wilkes County, NC, 2009	Before Project Lazarus	46.6
		North Carolina, 2009		11.0
Bird[128]	Opioids	European Union,[n] 1990s	Combination of 6 European cohorts[n]	870 (95% CI = 810, 940; converted)
Bargagli et al.[129]	Opioids	Barcelona, Spain, 1990	Cohorts recruited through EMCDDA protocol	1296 (converted)
		Denmark, 1990		707 (converted)
		Dublin, Ireland, 1990		309 (converted)
		Lisbon, Portugal, 1990		112 (converted)
		London, England, 1990		737 (converted)
		Rome, Italy, 1990		664 (converted)
		Vienna, Austria, 1990		661 (converted)

Continued

TABLE 3—*Continued*

Clausen et al.[130]	Opioids	Norway, 1997–2003	3789 opioid-dependent users[o]	2100 (converted) after treatment
Shah et al.[131]	Opioids	England and Wales, 1993–1998	Coroners' files; men	3.7 (converted)
			Coroners' files; women	0.94 (converted)
Scott et al.[95]	Illicit opioids	Chicago, IL, 2002[p]	Illinois master death files, 1999–2003, and Chicago Real Time Death Surveillance System 2003[p]	33.0–35.0
Morgan et al.[132]	Antidepressants	England and Wales, 1993	Coroners' files	0.9 (converted; age-adjusted)
		England and Wales, 2002		0.7 (converted; age-adjusted)
Rocchi et al.[133]	Illicit drugs	Italy, 1984–2000	Direzione Centrale per i Servizi Antidroga of the Italian Ministry of the Interior; men aged 15–44 y	6.6 (range = 1.6–11.3) avg per year
			Direzione Centrale per i Servizi Antidroga of the Italian Ministry of the Interior; women aged 15–44 y	0.7 (range = 0.3–1.1) avg per year
Fischer et al.[134]	Fentanyl	Ontario, 2009	Provincial coroners' data (all standardized)	0.44
		British Columbia, 2009		0.11
	Hydromorphone	Ontario, 2009		0.24
		British Columbia, 2009		0.45
	Morphine	Ontario, 2009		0.55
		British Columbia, 2009		2.94
	Oxycodone	Ontario, 2009		1.09
		British Columbia, 2009		0.70

Note. ALIVE = AIDS Linked to the Intravenous Experience; CDC = Centers for Disease Control and Prevention; CI = confidence interval; COBRA = Cost-Benefit and Risk Appraisal of Substitution Treatments study; EMCDDA = European Monitoring Centre for Drugs and Drug Addiction; IDU = injecting drug user; NVSS = National Vital Statistics System; NYC = New York City; WISQARS = Web-Based Injury Statistics Query and Reporting System; WONDER = Wide-Ranging Online Data for Epidemiologic Research.

[a]All substances = opioid and nonopioid substances, both pharmaceutical and illicit, including alcohol.

[b]Division of Vital Statistics of the US Public Health Service, death certificates, and Drug Enforcement Administration's annual budget.

[c]Scottish Drug Misuse Database cohort (treatment sample), matched with General Register Office for Scotland.

[d]Retrospective, population-based review of medical examiner cases in the Office of the Medical Examiner.

[e]National sample of 48 771 sentenced prisoners released during 1998–2000 with all recorded deaths included to November 2003.

[f]All unnatural, unexpected, or unattended deaths in the province (n = 904).

[g]All cases of fatal accidental drug overdose occurring in individuals aged 15–64 years.

[h]Users were identified through records in Stockholm in 1967; these individuals were followed in registers recording mortality and cause of death and in patient care stays until 2003.

[i]UFO ("U Find Out") Study comprised 644 injection drug users aged < 30 y, recruited by peer outreach workers with study invitation cards and flyers, contacts with youth-friendly neighborhood groups and community providers, and word of mouth; had to have self-reported use of injection drugs in the past 30 days.

[j]Collaborative Injection Drug Users Study comprised community-based, recent onset (< 5 y) injection drug users aged 18–35 years (n = 2089) from 5 US cities: Baltimore, MD; Chicago, IL; Los Angeles, CA; New Orleans, LA; and New York, NY.

[k]Self-referral and street outreach from the Downtown Eastside, one of Vancouver's poorest neighborhood: injection drug users aged 14–29 y (n = 572).

[l]Australian Treatment Outcome Study cohort consists of entrants to treatment of heroin dependence in opioid maintenance, detoxification, and residential rehabilitation; in addition, a group of heroin users not currently in treatment were recruited from needle and syringe programs in the regional health areas from which treatment entrants were recruited.

[m]Population-based (all state residents who died of unintentional pharmaceutical overdoses), observational study using data from medical examiner, prescription drug monitoring program, and opioid treatment program records.

[n]Combination of 6 European cohorts who were recruited according to a common EMCDDA protocol from drug treatment agencies in Barcelona, Spain; Denmark; Dublin, Ireland; Lisbon, Portugal; Rome, Italy; and Vienna, Austria.

[o]3789 opioid-dependent users who applied for and were accepted for opioid maintenance therapy (cross-linked with the Norwegian death register).

[p]Manually screened death certificates from the Illinois Department of Public Health master death files, 1999–2003, and the Chicago Real Time Death Surveillance System 2003. These communities' average poverty rate is 43%, 2 times that of the rest of the city.

Several studies reported on overdose mortality rates stratified by gender. Female-specific population-based overdose mortality rates reported included 9.8 in the United States, 0.94 in England and Wales, 0.7 in Italy, and 590 among recently released female prisoners.[6,106,131,133] Male rates were 3.7 in England and Wales, 6.6 in Italy, and 520 among recently released male prisoners.[106,131,133] Generally, death rates were higher among men than women, with the exception of recently released prisoners.

Among samples that included only drug users, overdose mortality rates were as high as 451.8,[115–117] and all-cause mortality rates ranged from 277 to 1368.[56,114,118] Among treatment-based samples, rates of drug-related deaths ranged from 309 to 2100.[41,104,124,128–130] Among samples of HIV-positive individuals, overdose death rates were 1120 to 1390.[119,120]

Correlates

Type of drug. Substances most commonly associated with overdose include cocaine, nonopioid analgesics (i.e., nonsteroidal anti-inflammatory drugs), and opioids—a class of drug that includes heroin, as well as prescription opioids such as morphine, methadone, codeine, and oxycodone. Some findings on how class of drug used affects overdose outcome are highlighted here.

Cocaine was one of the major drivers of overdose in the 1990s and early 2000s, especially in urban areas such as New York City.[22,23] In a study of witnessed overdoses in New York City in the early 2000s, powdered cocaine use predicted fatality among respondents' reported last witnessed overdose.[17] However, a shift toward opioids has occurred worldwide throughout the past several years.[135]

In a study of fatal overdoses in Connecticut, 77% of accidental overdose deaths from 1997 to 2007 involved opioids.[90] Opioid deaths were also more likely to involve alcohol and benzodiazepines.[2,85,90] Several articles focused on fentanyl, an opioid receptor agonist that is used as a filler for street heroin (or laced into heroin and cocaine) and has been more frequently prescribed in recent years.[136,137] Fentanyl is estimated to be 80 times more potent than morphine, so a small change in dosage may be fatal. Compounding this issue, many narcotic drug screens do not routinely screen for fentanyl.[138] Only 1 of the studies that included prescription medications[69] differentiated between those who experienced overdoses secondary to nonmedical use (i.e., using in larger amounts than prescribed or not prescribed for them) and had been prescribed these drugs versus those who experienced overdoses but had never been prescribed these drugs. Of the 596 respondents included in this study, 72.8% had already been prescribed in their lifetime prescription opioids, 45.5% had already been prescribed prescription tranquilizers, and 45.1% had already been prescribed prescription stimulants. None of the mortality articles included in our review had information on whether those who died because of overdoses secondary to prescription drug use had been using these drugs for therapeutic purposes.

Whether drugs are taken in pure form on their own or combination form (including mixed with alcohol) is important.[16,77] "Polydrug" use is associated with a much higher risk of death from overdose; a study of opioid overdoses presenting to an emergency department in Switzerland found that up to 90% of patients tested positive for multiple drugs.[139] According to the New York City Department of Health and Mental Hygiene, about 98% of overdose deaths that occur in the city involve more than 1 substance.[140] In addition, a review of Australian national coroner's records from 2000 to 2007 found that 72% of drug-related deaths in released prisoners involved polydrug use.[141]

For studies based on interviews about personal overdose experiences or witnessed overdoses, we cannot know with certainty exactly what type of drug or how many the person overdosed on, but rely on participant responses (e.g., Tracy et al.[16]). These types of studies also often have inclusion criteria such as had to have injected heroin within the past 2 months[15] or had to have injected heroin or cocaine during the preceding 30 days,[37] which give us some indication of what drug was likely used, but it is not always specified. Some were treatment samples of specific types of drug users[41,43] in which we generally assume for simplicity that if they were heroin injectors, they overdosed on heroin. Some studies do specify "heroin only," for example, or differentiate between "heroin only" and "heroin and other drugs,"[49] though, again, these are often based on self-report. Others still differentiate between single drugs and combination, but are based on autopsy findings or a mix of autopsy findings and circumstances of the fatality that we can be a little more sure about.[113] Most of the larger countrywide studies on mortality or trends look at overall deaths or hospitalizations, not distinguishing between type of drug (e.g., White et al.[11]).

Setting or regional differences. Drug overdose is not just an urban problem, even though historically more emphasis has been placed on urban areas.[142–144] In recent years, rural areas have seen rapid increases in rates of nonmedical prescription drug use and overdose: in rural Virginia between 1997 and 2003, fatalities attributed to overdose increased by 300% (prescription opioids and benzodiazepines were more prevalent than illicit drugs).[76] In Utah, prescription opioid deaths increased fivefold during 2000 to 2009.[28] Furthermore, prescription drug overdose is now the leading cause of injury death in Ohio, with particularly high rates in the rural Appalachian areas of the state.[84]

In addition, the setting and circumstances of a drug overdose can tell us a lot about potential outcomes. In a study of fatal overdose in New York City in 1996, deaths were more likely to occur in neighborhoods in the top decile of income inequality than in more equitable neighborhoods.[145] This relationship was partially explained by the level of disorder in the environment and the quality of the built environment. When compared with nonoverdose but unintentional deaths, prescription opioid overdose deaths from another study in New York City were more likely to occur in lower-income and "fragmented" neighborhoods, but when compared with heroin fatalities, they were more likely to occur in higher-income and less-fragmented neighborhoods.[146] One explanation for this is that higher-income neighborhoods offer a larger supply of prescription opioids through pharmacies and physicians that is not present in more disadvantaged, primarily minority neighborhoods. A study in 10 Spanish

cities from 1996 to 2003 found that male overdose deaths were more common in cities with high levels of socioeconomic inequality.[147]

The physical settings in which users inject also matter. A Vancouver study estimated that users who injected in public places (vs those who injected in private settings) were 4.7 times more likely to experience a nonfatal overdose.[19] A study by Bohnert et al. on policing and risk of overdose in New York City found that fatal overdoses were more likely to occur in secluded public places, such as abandoned buildings.[20] This is likely attributable to the fact that it is more difficult to find help when someone overdoses, and may be a result of fear of heavy policing in urban areas. Another study that investigated risks of heroin overdose noted injection in an "unusual place" (defined by each individual according to his or her injecting habits) as a risk factor for overdoses.[21] One explanation presented for this phenomenon is that tolerance is based on Pavlovian conditioning of cues, and when a user of typically high tolerance injects in an unusual circumstance, they lack the cues that they usually associate with a drug's effect, causing their tolerance to fail.[148]

Characteristics of the user. Lastly, characteristics of the drug user are important to consider as correlates for drug overdose. One characteristic of note is gender. Men are more likely to self-report nonmedical use of prescription drugs, yet more women are more often prescribed drugs prone to abuse.[149,150] This might be because of the fact that many common forms of pain such as osteoarthritis, fibromyalgia, lower-back pain, and shoulder pain are more prevalent among women, and women also report higher intensity of pain from these conditions.[151,152] The US Centers for Disease Control and Prevention reported that the proportion of drug overdose deaths caused by prescription opioids was highest among women aged 45 to 54 years and among American Indian or Alaska Natives and non-Hispanic White women.[153] A study in Australia showed a 70-to-30 male-to-female ratio of nonfatal heroin overdose.[142]

Another commonly studied correlate is race/ethnicity. A review of coroner case files from British Columbia from 2001 to 2005 found that First Nations individuals had higher rates of mortality from overdose.[108] An investigation of fatal accidental drug overdose in New York City between 1990 and 1998 found that overdose deaths were consistently higher among non-Hispanic Blacks and Hispanics compared with non-Hispanic Whites. In addition, cocaine was more common among non-Hispanic Black decedents, whereas opioids and alcohol were more common among Hispanic and non-Hispanic White decedents.[22] On the other hand, rates of prescription opioid deaths are higher among non-Hispanic Whites than among respondents of other races/ethnicities.[153]

Other factors associated with increased risk of nonfatal overdose found in the literature review included belonging to a lower income group while growing up, not graduating high school, being a smoker, having ever received care at a psychiatric facility, ever witnessing a family member overdose, being prescribed tranquilizers, having cocaine dependence, and injecting in the past 90 days.[28,36,69,154]

Certain subgroups of the population are especially prone to overdose risk, including homeless individuals, HIV-positive individuals, and recently released prisoners.[65,120,155,156] Individuals who have recently attended substance abuse treatment or been released from incarceration are at increased risk of overdose, often because they have lost tolerance for their usual doses.[26,157] Overdose is also significantly associated with psychiatric disorders, suicidal ideation, and attempted suicide.[67,158] Lastly, duration of drug use and reports of previous overdose episodes are associated with overdose.[159,160]

DISCUSSION

We systematically synthesized the peer-reviewed literature to document the global epidemiological profile of unintentional drug overdoses, and the prevalence, time trends, mortality rates, and correlates of drug overdoses. We found, first, wide variability in the lifetime prevalence of experiencing a nonfatal overdose and in mortality rates attributable to overdoses, depending on the study setting. Second, the majority of studies on longitudinal trends of overdose death rates or overdose-related hospitalization rates showed increases in overdose death rates and in overdose-related hospitalization rates across time, which have led to peaks in these rates now. In particular, an overall trend of increasing deaths from prescription opioid use and decreasing deaths from illicit drug use in the past several years has been noted across most of the literature.[80–82,89,90,96,97,99,100] Third, with the increase in prescription opioid overdose deaths, drug overdose is no longer just an urban problem: rural areas have seen an important increase in overdose deaths. Fourth, cocaine, prescription opioids, and heroin are the drugs most commonly associated with unintentional drug overdoses worldwide and the demographic and psychiatric correlates associated with unintentional drug overdoses are similar worldwide. However, more studies examining these correlates are needed from non–English-speaking countries.

Drug overdose is an important, yet inadequately understood, public health problem. A review of existing studies points to several key methodological issues that future studies need to address and limitations in extant studies. Methodological issues include enhancing data collection methods on unintentional fatal and nonfatal overdoses, and collecting more detailed information on drug use history, source of drug use (for prescription drugs), and demographic and psychiatric history characteristics of the individual who overdosed. For example, future studies could employ consistency check strategies to compare medical examiner information on fatal overdoses with available medical records and information from the deceased individuals' family members.

Future data collection efforts could also include more detailed questions when interviewing individuals who report nonfatal overdoses, and check consistency of such information with hospital discharge data and information from family or other third parties (e.g., friends who witnessed the overdose episode). The field still also lacks studies in rural areas as well as longitudinal studies of population-based drug users (i.e., non–treatment samples) in multiple urban and rural areas that would provide us with comparable prevalence estimates across different contexts.

In addition, several of the selected studies did not disclose how

they defined nonfatal overdoses to study respondents,[33,34,37] simply mentioning that they asked them if they had ever experienced or witnessed an overdose, which could be somewhat misleading and biased. On the other hand, it should be noted that, among the studies that provided information on the definition of nonfatal overdoses, the definition of nonfatal overdoses was overall extremely consistent and standardized across the reviewed studies, similar to the definition we present in the introduction of this review.[12,14–17,36,39,40]

The marked increase in prescription opioid overdoses described in the studies reviewed is likely attributable to a rapid increase in sales of prescription opioids during the past decade; the quantity of prescription opioids sold to pharmacies, hospitals, and doctors' offices in the United States was 4 times larger in 2010 than in 1999.[8] The increase in overdoses caused by prescription opioid use in the United States parallels the increase in the availability of prescription opioids since the early to mid-1990s in the United States.[90] As described in one of Nora Volkow's recent presentations to the US Senate:

> The number of prescriptions for opioids (like hydrocodone and oxycodone products) have escalated from around 76 million in 1991 to nearly 207 million in 2013, with the United States their biggest consumer globally, accounting for almost 100 percent of the world total for hydrocodone (i.e., Vicodin) and 81 percent for oxycodone (i.e., Percocet).[161(p3)]

There is a need to invest in research to understand the distinct determinants of this type of overdose worldwide. Several other countries need to collect in a systematic and continuous fashion such data on sales of prescription opioids and other prescription drugs, nonmedical use of prescription drugs, and hospitalization secondary to overdoses on prescription drugs. Moreover, there is the need for future studies to further investigate whether those who overdose while using prescription medication had been prescribed these drugs recently or in the past because only 1 of the reviewed studies included this information.[69]

Finally, the sparse evidence on the environmental determinants of overdose suggest a need for research that will inform the types of environmental interventions we can use to prevent drug overdose. A combination of studies on individuals who overdose and the settings where overdoses occur will help us better tailor interventions to the types of strategies that are most likely to have a major impact on this epidemic.

Limitations of the reviewed studies are also noted. First, most studies did not collect information on the sources of drug used, which can provide insights into the ways individuals learn about and acquire drugs, and can thus inform prevention opportunities. Drugs can be acquired from family, friends, and drug dealers, but they can also be prescribed for legitimate medical reasons (in the case of prescription drugs). More studies that investigate prescribing patterns, such as the article by Logan et al. on potentially inappropriate prescriptions given in the emergency department,[162] are needed. Moreover, only about a third of the mortality rate studies, half of trends studies, and one sixth of the prevalence studies stratify results by specific types of prescription drugs.

Second, it is already well established that there might be an underreporting of intentional overdoses, because when substance users are asked whether their overdose was or was not intentional, most report it as unintentional.[29,163,164] In our review, we focused on unintentional overdoses, but there is the possibility that some of these overdoses were truly intentional.

Third, because substance users who experience an overdose are usually polydrug users, it is very difficult to distinguish which and how many drugs were used before an overdose episode.[165–168] Because of the high prevalence of multiple drugs being present in overdoses,[11,139] it is hard to tease out the effect of one drug over another. Overall, there is a mix of how well studies differentiate, but many aim to show an overall measure of burden of this issue, not truly trying to make a causal association with any 1 type of drug.

Fourth, studies have shown that forensic toxicology laboratories are limited in the number of drugs for which they can screen and that drug levels can change postmortem.[165–168] Further complicating this issue is the fact that data collected by medical examiners and coroners are usually inadequate, incomplete, and inconsistent with regard to polydrug use, estimated drug dosage (when, for instance, the individual had a legitimate prescription for at least 1 of the drugs involved in the fatal overdose episode—e.g., a legitimate opioid prescription), and patient characteristics.[169]

Fifth, if we are to identify potential avenues to prevent drug overdose, more concerted investment needs to be made to understand the environmental drivers of overdose risk, and the individual and interpersonal mechanisms whereby environmental characteristics can increase the risk for overdose. This is particularly important for overdose risk in rural areas, as the bulk of the literature on environmental determinants of overdose has focused on urban areas. This also has important implications for prevention and intervention strategies that need to focus on harm reduction strategies such as the availability of safe injection facilities or mobile safe injection facilities where individuals can inject preobtained drugs under the supervision of a medical doctor, such as facilities that exist in Canada and in some European countries,[19] while also offering them treatment for their drug-using behavior. ■

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Contributors

S. S. Martins and S. Galea designed the study. S. S. Martins directed L. Sampson on the literature review, and wrote the first full draft of the manuscript. L. Sampson conducted the literature review and prepared the Methods and the Results sections of the text. S. Galea critically reviewed all drafts of the article. M. Cerdá helped write the Discussion section and critically reviewed all other sections of the article.

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Human Participant Protection

The article is a review of already published articles and considered non–human participant research by Columbia University's institutional review board.

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