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IN FOCUS THE OPIOID CRISES

WORLD DRUG REPORT 2020

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EXPLANATORY NOTES

The designations employed and the presentation of the material in the World Drug Report do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Countries and areas are referred to by the names that were in official use at the time the relevant data were collected.

Since there is some scientific and legal ambiguity about the distinctions between "drug use", "drug misuse" and "drug abuse", the neutral term "drug use" is used in the World Drug Report. The term "misuse" is used only to denote the non-medical use of prescription drugs.

All uses of the word "drug" and the term "drug use" in the World Drug Report refer to substances controlled under the international drug control conventions, and their non-medical use.

All analysis contained in the World Drug Report is based on the official data submitted by Member States to the UNODC through the annual report questionnaire unless indicated otherwise.

The data on population used in the World Drug Report are taken from: World Population Prospects: The 2019 Revision (United Nations, Department of Economic and Social Affairs, Population Division).

References to dollars ($) are to United States dollars, unless otherwise stated.

References to tons are to metric tons, unless otherwise stated.

The following abbreviations have been used in the present booklet:

alpha-PVP	*alpha*-pyrrolidinovalerophenone
APAAN	*alpha*-phenylacetoacetonitrile
ATS	amphetamine-type stimulants
CBD	cannabidiol
DEA	Drug Enforcement Administration
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
Europol	European Union Agency for Law Enforcement Cooperation
GDP	gross domestic product
INCB	International Narcotics Control Board
INTERPOL	International Criminal Police Organization
LSD	lysergic acid diethylamide
MAPA	methyl alpha-phenylacetoacetate
MDA	methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
MDPV	methylenedioxypyrovalerone
4-MEC	4-methylethcathinone
3-MMC	3-methylmethcathinone
4-MMC	4-methylmethcathinone
NPS	new psychoactive substances
PCP	phencyclidine
P-2-P	1-phenyl-2-propanone
PMK	piperonyl methyl ketone
S-DDD	defined daily doses for statistical purposes
THC	Δ-9 – tetrahydrocannabinol
UNODC	United Nations Office on Drugs and Crime

THE OPIOID CRISES

Among people who use drugs, the non-medical use of opioids has always been associated with the most negative health consequences attributed to any drug type. The non-medical use of opioids has been responsible for the majority of drug-related deaths since these have been globally recorded. In the last few years, however, new threats have emerged in relation to opioids that have escalated the number of drug overdoses in some regions and rapidly increased the number of people with drug use disorders in others. This new opioid crisis is related to the non-medical use of pharmaceutical opioids. Whereas heroin remains the opioid of major concern for the great majority of countries and the population of opioids users, in some countries and regions the non-medical use of pharmaceutical opioids has triggered new health threats.

The non-medical use of pharmaceutical opioids is not a new phenomenon. It has been observed for decades as part of the polydrug use pattern among high-risk or regular opioid users. What characterizes the most recent opioid crisis is the emergence of non-medical use of pharmaceutical opioids as the main phenomenon, leading to alarming rates of dependence and overdose deaths at the national level. The subregions most affected by this crisis are North America and West, Central and North Africa, where different opioids and different dynamics are driving the threat. In North America, the introduction of fentanyl and its analogues (fentanyls) in the drug market has resulted in a syndemic of use of opioids characterized by an unprecedented increase in opioid overdose deaths. In West, Central and North Africa and the Middle East, tramadol – a pharmaceutical opioid not under international control – has emerged as a major opioid of concern. The drug, in addition to being diverted from the legal market, is mainly trafficked into those subregions in dosages higher than what is prescribed for pain management, with an increasing number of people with tramadol use disorder entering treatment.

The dynamics and the recorded consequences of tramadol in Africa and of fentanyls in North America are different. There are serious information gaps with respect to the tramadol market and its health consequences in Africa. The rapid spread of non-medical use of tramadol is evident, but there is no measurable information on its impact on health (or on drug-related deaths and overdoses), whereas in North America the deadly consequences of the fentanyls have been well recorded and measured. Moreover, unlike tramadol, which is often chosen for use as the main compound, fentanyls are mixed in for use as adulterants in other drugs, with the result that users are often unaware that they are consuming them.

From what is known, it is possible to identify common threats and different dynamics in the two opioid crises, in Africa and in North America:

- The ease of manufacturing, easy accessibility and low-cost production make the illicit markets for tramadol and fentanyls substantially more profitable for traffickers than are other opioids such as heroin.
- The large-scale manufacture of tramadol and fentanyls for the illicit market started in a context of an absence of international regulations on tramadol and many fentanyl analogues or their precursors.
- The interchangeability (or substitution) of fentanyl and tramadol within the pharmaceutical and illicit drug markets makes it more difficult to address their misuse. Their non-medical use is also seen in the context of self-medication, and thus carries less stigma or is countered by lesser legal sanctions than is the case with other controlled drugs.

A key difference in the spread of the two opioids is that use of fentanyl is mainly supply-driven. In the case of tramadol, it is less clear. The market for non-medical use of tramadol in some areas may have started as a result of easy access in the unregulated pharmaceutical markets. Drug preference is to a large extent related to the availability of the drug more than to the individual liking of the substance used or misused, indicating that the tramadol crisis may have been mainly demand driven.[78] The health impacts of the surge in the two markets also appear

78 Mai Taha and others, "Cannabis and tramadol are prevalent among the first episode drug-induced psychosis in the Egyptian population: single center experience", *Reports: Medic Cases, Images and Videos*, vol. 2 (June 2019), p. 16.

to be different: the emergence of fentanyl has not increased the number of persons who use opioids, but it has driven up the number of overdoses among existing users. Tramadol, on the other hand, seems to have driven use among a wider segment of the population and in an increasing number of people in treatment, more than driving up the number of deaths, although reliable information on overdoses is not available for Africa.

The following sections of this chapter look at the market development of the two opioids, fentanyls and tramadol, with the aim of improving understanding of the factors that may have contributed to their spread, some of the potential threats posed by their misuse.

Opioid crisis in North America

The opioid crisis in North America has been characterized by the triple and interlinked epidemic of non-medical use of pharmaceutical opioids, use of heroin and use of fenatanyls (i.e., fentanyl and its analogues) that are mostly illicitly manufactured and are primarily sold as falsified pharmaceutical opioids or are laced with heroin or other drugs.

The opioid epidemic in the subregion has led to an increasing number of overdose in some geographical areas (western Canada and the eastern United States), although the epidemic now appears to be steadily expanding to other areas. Although geographically disconnected, the areas that were initially affected by the opioid crisis in Canada and the United States have experienced remarkably similar market dynamics, which can be broadly described in the following sequential steps:

(a) High rates of prescriptions for pharmaceutical opioids leading to diversion and an increase in the non-medical use of pharmaceutical opioids, opioid use disorders and an increase in opioid overdose deaths

(b) Regulations introduced to reduce diversion and non-medical use of pharmaceutical opioids (e.g., tamper-proof formulations to prevent injecting)

(c) Partial resurgence of heroin use, resulting in an increase in heroin overdose deaths from 2010 onwards, fentanyls introduced as an adulterant in heroin, and a further increase in heroin overdose deaths (from 2014 onwards), while the number of pharmaceutical opioid overdose deaths began to stabilize

(d) Fentanyl (illicitly manufactured in clandestine laboratories) and its analogues emerge as adulterants in heroin and stimulants (cocaine and methamphetamine) and are sold as falsified pharmaceutical opioids, resulting in massive increases in deaths attributed to fentanyls

(e) Fentanyls emerge as the dominant opioid in opioid overdose deaths, as well as contributing to overdose deaths attributed to other drugs

(f) Overdose deaths attributed to pharmaceutical opioids and heroin (alone) stabilize or show small declines

(g) Fentanyl-related deaths are the main contributor to total opioid overdose deaths; they continued to increase in 2018 although at a lower rate than previously

These dynamics are now gradually spreading outside the originally affected regions in both Canada and the United States. If the latest observed tail of the epidemic in some states of the United States is bringing a relative stabilization in the national total of overdose deaths, it is not yet clear whether this is a sign of the epidemic having plateaued. If similar dynamics and intensity of the epidemic, as were experienced initially in the states in the East of the United States and the Western provinces of Canada, extend to other states or provinces, the associated harm, including overdose deaths, may continue rising.

The scientific literature has attempted to understand the reasons for the sudden rise of fentanyls in pre-existing opioid markets. It seems that an interplay between a number of external factors and local market dynamics played a role in the spread of the opioid crisis in North America. Some of the factors that have led to the rise and continued presence of fentanyls include: (a) the diffusion of simpler and more effective methods of manufacture of synthetic opioids and their analogues (primarily fentanyls); (b) a lack of effective control of precursors and oversight of the manufacture industry; (c) expanding distribution networks; (d) reduced smuggling risks because of new methods of trafficking within the expanded licit trade; and (e) pre-existing market

conditions (demand for opioids and potential supply shocks).[79]

What seems clear is that the fentanyls market is supply-driven. While some authors have documented a niche market of users among whom there is a conscious demand for fentanyls, most opioid or stimulant users are not looking for fentanyls specifically and are often unaware of their use as an adulterant.

Developments in the United States

Opioid overdose deaths

In the United States, there are early signs of stabilization of the opioid crisis, although misuse levels remain high. One of the major adverse health outcomes of the opioid crisis has been the unprecedented number of fatal overdose cases linked to opioids. Between 2007 and 2018, the total number of all overdose deaths in the United States nearly doubled while the number of overdose deaths attributed to opioids increased 2.5-fold, from 18,515 deaths in 2007 to nearly 47,000 deaths in 2018. It is important to keep in mind that there is more than one drug type involved in most overdose cases. Furthermore, even for opioids there is a considerable mixing of different opioids along with other drugs. For instance, in 2018 more than one third of overdose deaths involving pharmaceutical opioids and more than half of those involving heroin also involved fentanyls.

By December 2018, the number of overdose deaths had declined by 4 per cent, and overdose deaths attributed to opioids and heroin had declined by less than 2 and 3 per cent, respectively, compared with a year earlier.[80] The major decline in overdose deaths from 2017 to 2018 is clearly seen in overdose deaths attributed to pharmaceutical opioids, which declined by 12 per cent.

The decline in overdose deaths attributed to opioids could in part be attributed to the community-wide availability of naloxone for the reversal of opioid overdose, in addition to a continued decline from 2012 to 2018 in overall opioid prescription rates. The rate of prescription of opioids in the United States fell to 51.4 prescriptions per 100 persons (a total of more than 168 million opioid prescriptions) in 2018 from a peak of 81.3 opioid prescriptions per 100 persons (or 255 million opioid prescriptions) in 2012. The opioid prescription rate in the southern United States remains high, however, with most states in the region reporting opioid prescription rates of 64 or more per 100 persons in 2018.[81] A number of factors at work, including advertising by the pharmaceutical industry, physicians' prescription practices, dispensing and medical culture and patient expectations have, since the new millennium, resulted in high prescription rates and dosages of opioids given for an extended duration of care, primarily for the management of acute to chronic non-cancer pain.[82] These practices have also enabled the diversion and misuse of pharmaceutical opioids, together with a greater risk of opioid use disorders among those with a legitimate prescription.[83]

Nevertheless, these gains in the reduction of overdose deaths attributed to pharmaceutical opioids have been partly offset by the continuing increase in deaths attributed to synthetic opioids and, in particular, those attributed to fentanyls, which have increased by 10 per cent over the past year. In United States overdose data, for instance, fentanyl is generally designated as "illicitly manufactured fentanyl" because it is not diverted from licit channels but is either trafficked into the country or, to a lesser extent, manufactured locally in clandestine laboratories.[84] Overall, in 2018 overdose deaths attributed to synthetic opioids, comprising mainly

79 Bryce Pardo and others, *The Future of Fentanyl and other Synthetic Opioids* (Santa Monica, California, RAND Corporation, 2019).

80 Holly Hedegaard and others, "Drug Overdose Deaths in the United States, 1998-2019", National Center for Health Statistics Data Brief, no 356, Centers for Disease Control and Prevention, National Center for Health Statistics, January 2020.

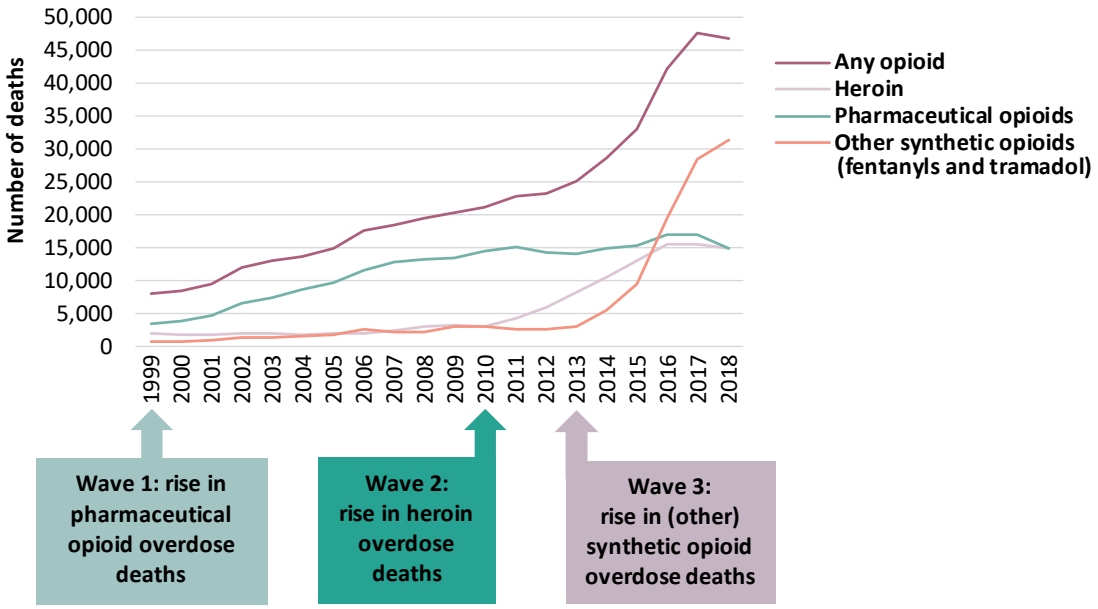
81 Centers for Disease Control and Prevention, US Opioid Prescribing Rate Maps. Available at https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html.

82 Benedikt Fischer and others, "Non-medical use of prescription opioids and prescription opioid-related harms: why so markedly higher in North America compared to the rest of the world?", *Addiction*, vol. 109, No. 2 (February 2014), pp. 177–181.

83 See also *World Drug Report 2019: Depressants* (United Nations publication, Sales No. E.19.XI.8 (Booklet 3)).

84 Fentanyl diverted from the legitimate market, prescribed in the form of transdermal patches, or lozenges, but is of only limited importance for the United States. United States, Department of Justice, DEA, *2018 National Drug Threat Assessment* (October 2018).

FIG. 27 Opioid overdose deaths in the United States, 1999–2018



Source: United States, Centers for Disease Control and Prevention, National Center for Health Statistics, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER), "Multiple cause of death 1999–2018".

fentanyls, accounted for nearly half of the total overdose deaths in the United States. Among the reasons for the high number of overdose deaths attributed to fentanyls are their often small lethal doses relative to other opioids: fentanyl, for example, is approximately 100 times more potent than morphine, and carfentanil may be as much as 10,000 times more potent than morphine for an average user. A lethal dose of carfentanil for a human can be as low as 20 micrograms.

The rapid expansion of fentanyl use in the United States is also visible in the data on seizures and the drug samples analysed, with a considerable increase since 2014 in the number of samples identified as fentanyl. In 2018, fentanyl accounted for 45 per cent of the pharmaceutical opioids that were identified in different samples, while oxycodone accounted for 14 per cent. Furthermore, while over the years fentanyl has been the predominant substance seized of the overall group of fentanyls (the structurally related opioids), those fentanyl analogues have also proliferated in the United States. As a percentage of all pharmaceutical opioid samples seized and identified in 2018, some fentanyl analogues were notable: acetylfentanyl accounted for nearly 4 per cent of identified samples, and fluoroisobutyrylfentanyl, methoxyacetylfentanyl and cyclopropylfentanyl each accounted for less than 1 per cent.

Regional variations in opioid overdose deaths

The opioid crisis is concentrated differently across geographical regions of the United States. Opioid overdose deaths are consistently higher than the national average, which was 14.6 per 100,000 population in 2018, in the states east of the Mississippi river, including West Virginia (42.4 per 100,000 population in 2018), Maryland (33.7 per 100,000 population), New Hampshire (33.1 per 100,000 population) and Ohio (29.6 per 100,000 population), and lower than the national average in the western states of the United States.[85] This concentration of opioid overdose deaths becomes more evident in the case of overdose deaths attributed to fentanyls. Many states east of the Mississippi river, such as West Virginia (34 per 100,000), New Hampshire (31.3 per 100,000), Ohio (25.7 per 100,000),

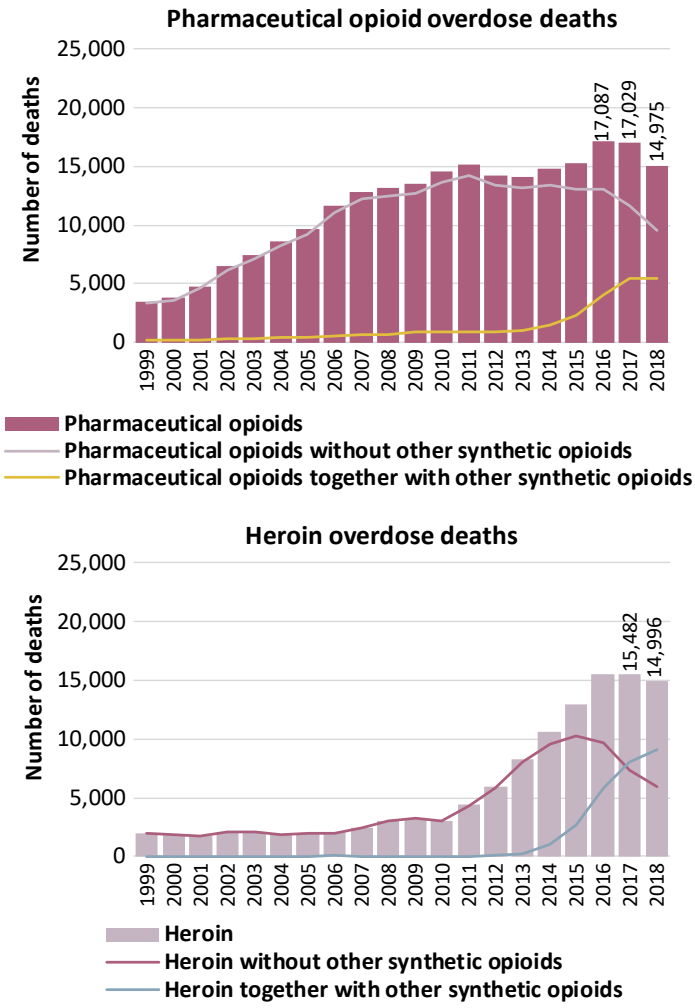
85 United States, Centers for Disease Control and Prevention, National Center for Health Statistics, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER), "Multiple cause of death 1999–2018".

and the District of Columbia (22.6 per 100,000) had rates of overdose deaths attributed to synthetic opioids that were multiple times higher than the national average of 9.9 deaths per 100,000 population in 2018. In the western United States, the rates are much lower: in 2018, overdose deaths attributed to fentanyls amounted to 2.2 per 100,000 population in California and 2.9 per 100,000 population in Washington.

The synthetic opioid crisis, driven primarily by fentanyl and fentanyl analogues, appears to be migrating from the eastern states of the United States to the western states. The western states have reported the lowest overdose deaths attributed to synthetic opioids since 2011. Nevertheless, the rates of synthetic opioid overdose deaths in the western states have increased by 3.5-fold over the past five years. While the rates of overdose deaths attributed to synthetic opioids are persistently higher in the eastern states than in other parts of the country, in 2018 many of the states east of the Mississippi river that had a high prevalence of synthetic opioid use (mainly fentanyls) reported a decline in overdose deaths attributed to fentanyls. The largest decline was reported in Ohio (a decline of 21 per cent), followed by Georgia (a decline of 17 per cent), while other states such as Missouri, Tennessee, Illinois and South Carolina showed a significant increase in the number of synthetic opioid overdose deaths between 2017 and 2018. On the other hand, many states west of the Mississippi river, while still reporting low numbers of fentanyl-related overdose deaths, recorded an increase in such overdose deaths over the period 2017–2018. Arizona recorded a 93 per cent increase, followed by California (69 per cent), Washington (53 per cent) and New Mexico (46 percent).[86]

In some of the states, such as New Hampshire in the north-eastern United States, where fentanyl first appeared, mixed with other substances, fentanyl has now emerged as a standalone substance for use rather than as an adulterant. Synthetic opioids predominate overdose there despite a considerable reduction in overdose deaths attributed to pharmaceutical opioids and heroin.

FIG. 28 United States: number of overdose deaths attributed to pharmaceutical opioids and heroin, 1999–2018

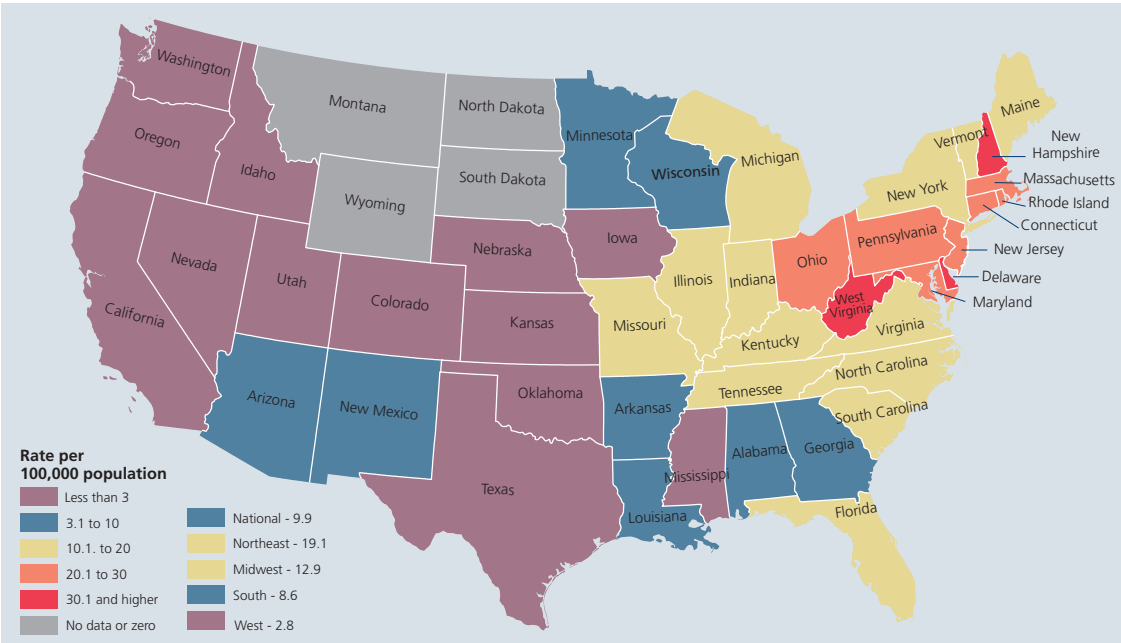


Source: United States, Centers for Disease Control and Prevention, National Center for Health Statistics, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER), "Multiple cause of death 1999–2018".

The uneven spread of fentanyl in the United States is also visible in supply indicators

The differential availability of synthetic opioids and evolution of the synthetic opioid crisis are also visible in seizure data. Data on the steady increase in fentanyl samples seized and analysed suggest that the availability and supply of fentanyl continues to be more concentrated east of the Mississippi river than west of it. In 2018, fentanyl accounted for the highest percentage of seized pharmaceutical opioid

MAP 2 Synthetic opioid overdose deaths, age-adjusted rates per 100,000 people, in the United States, 2018

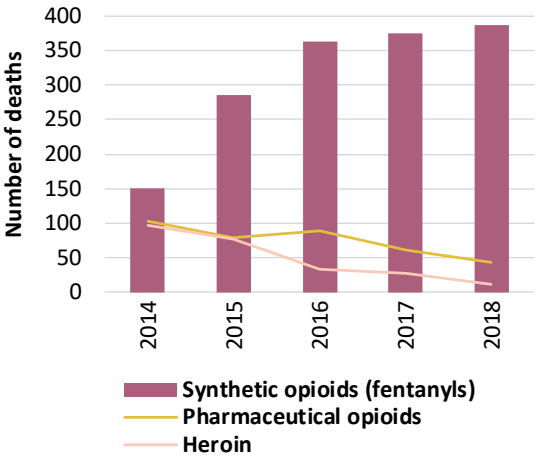


Source: United States, Centers for Disease Control and Prevention, National Center for Health Statistics, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER), "Multiple cause of death 1999–2018".

Note: Alaska and Hawaii are not shown because valid estimates do not exist for these two States.

The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations.

FIG. 29 New Hampshire, United States: number of opioid overdose deaths, by type, 2014–2018



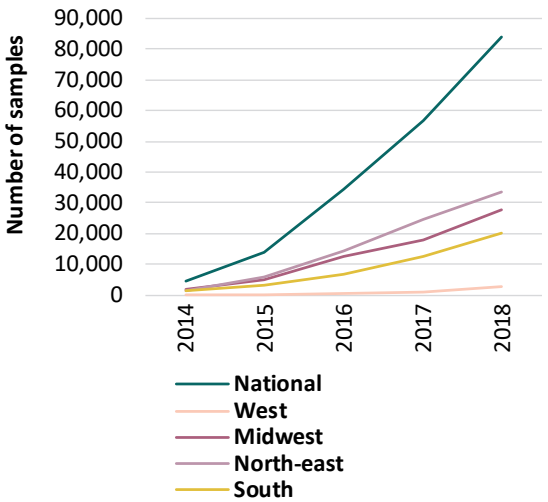
Source: United States, Centers for Disease Control and Prevention, National Center for Health Statistics, Wide-ranging Online Data for Epidemiologic Research (CDC WONDER), "Multiple cause of death 1999–2018".

samples in the north-eastern United States and the Midwest (40 per cent and 33 per cent, respectively), which are regions of the country with a higher prevalence of heroin use and of overdose deaths attributed to synthetic opioids. Although fentanyl samples that were seized and analysed in the western parts of the country make up only 3 per cent of the total samples seized and analysed nationally, over the years those parts of the country are actually where the share has increased the most.[87]

It is not clear why synthetic opioids are differentially available in the United States. It may in part be an artefact of regional differences in user preferences, or it may be a business model that is more successful in some markets than others. It has also been argued that one regional difference driving the

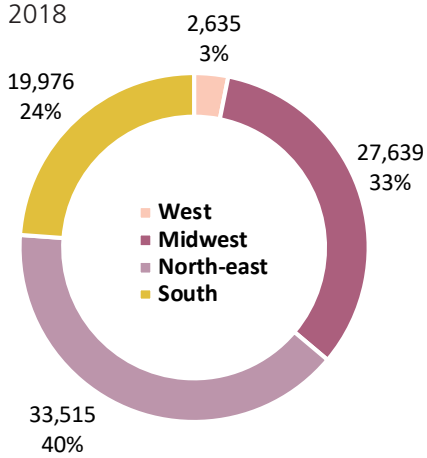
87 While the reporting of the National Forensic Laboratory Information System of fentanyl samples seized and analysed are spatially concentrated in the eastern regions of the United States, this concentration may also reflect the efforts of law enforcement authorities as well as the capacity of local laboratories to analyse the seized samples.

FIG. 30 Fentanyl samples submitted to and analysed by forensic laboratories, by region, United States, 2014–2018



Source: United States, Department of Justice, DEA, Diversion Control Division, National Forensic Laboratory Information System, reports for different years.

FIG. 31 Number and percentage of fentanyl submitted to and analysed by forensic laboratories, by region, United States, 2018



Source: United States, Department of Justice, DEA, Diversion Control Division, "National Forensic Laboratory Information System: NFLIS-Drug 2018 annual report" (Springfield, Virginia, 2019).

opioid crisis could be attributed to the predominant type of heroin available or supplied in the market. The western states of the United States are supplied with significant amounts of " black tar", a dark-coloured heroin (base) which is less often adulterated with fentanyls than white the powder form of heroin (hydrochloride), which is predominant in the markets of the north-eastern United States.[88, 89]

Overall deaths: apparent stabilization but potential for increase

Overall, the main impact of the overdose deaths in the United States, especially those due to synthetic opioids (including fentanyls), is seen in urban counties, where large fringe metro areas (i.e., counties with 1 million or more population), followed by medium-sized metro counties (those with a population ranging between 250,000 and 999,999), had the highest rates of synthetic opioid overdose deaths in 2018, at, respectively, 12.7 and 10.5 overdose deaths per 100,000 population.[90] The opioid overdose death rate continued to increase in those urban counties over the period 2017–2018

Another aspect that compounds the situation with drug overdose deaths is the contributing influence of multiple drugs, as there is more than one substance involved in most overdose deaths. The decision on which drug or drugs could have contributed to mortality is based on determining the presence of toxicologically meaningful levels of a drug or multiple drugs found during forensic examination. This is an important consideration, for example, in the western United States where psychostimulants such as methamphetamine contribute to a significant proportion of overdose deaths, while heroin-related and fentanyl-related overdose deaths are ranked second and third, respectively.[91] The latter two substances also contribute to a significant number of overdose deaths attributed to psychostimulants. As is the case with heroin- and pharmaceutical opioids-related overdose deaths, the increase in overdose deaths attributed to cocaine

88 United States, Congressional Research Service, "Heroin trafficking in the United States" (Washington D.C., 14 February 2019).

89 United States, Department of Justice, DEA, *2018 National Drug Threat Assessment.*

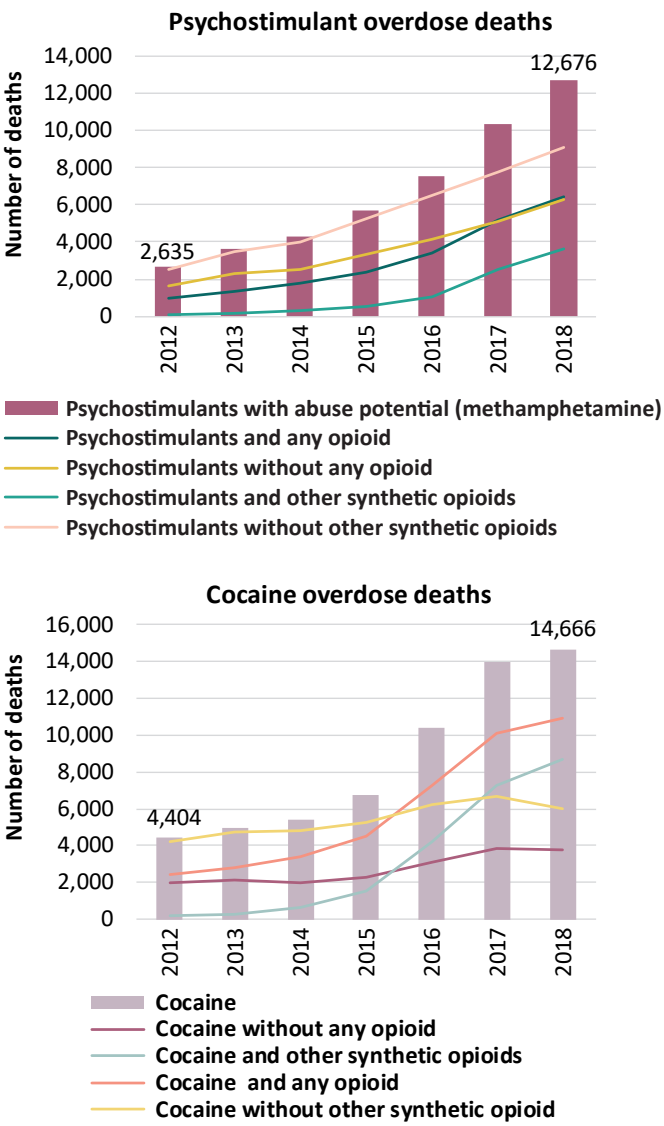
90 Nana Wilson and others, "Drug and opioid-involved overdose deaths – United States, 2017-2018" *Morbidity and Mortality Weekly Report*, March 2020;69 (11); pp.290–297.

91 Holly Hedegaard and others, "Regional differences in the drugs most frequently involved in drug overdose deaths: United States 2017", *National Vital Statistics Reports*, vol. 68, No. 12 (October 2019).

and psychostimulants (primarily methamphetamine) that has been observed across the United States is also associated, to a large extent, with the increasing co-involvement of synthetic opioids.

Over the period 2015–2018, the absolute number of overdose deaths attributed to cocaine more than doubled, with nearly 60 per cent of cocaine overdose deaths in 2018 involving synthetic opioids; similarly, overdose deaths attributed to psychostimulants (primarily methamphetamine) also more than doubled over the same period, with more than a quarter also involving synthetic opioids. Finally, there was also an increase in overdose deaths attributed to benzodiazepines in that same period, with nearly half of those deaths involving synthetic opioids. This suggests that people using drugs other than opioids as a primary substance are increasingly exposed to fentanyls and other potent synthetic opioids.[92]

FIG. 32 United States: overdose deaths attributed to cocaine and psychostimulants, with and without opioids, 2012–2018



Source: United States, Centers for Disease Control and Prevention, Wide-ranging Online Data for Epidemiologic Research, "Multiple cause of death (Detailed mortality), 1999–2018".

These indicators suggest that while there are early signs of a stabilization in the number of overdose deaths in the United States, deaths involving synthetic opioids continue to pose a threat to public health and safety, particularly as the use and availability of these substances continue to make their way westward and are incorporated into the heroin and non-opioid drugs market.

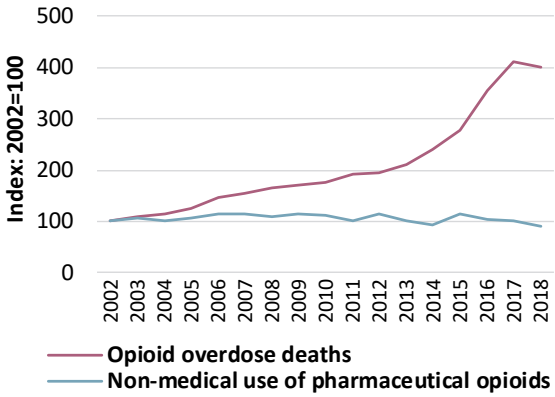
Opioids use appears to be stabilizing

In contrast to the changes observed in the number of opioid overdose deaths, the National Survey on Drug Use and Health suggests that the number of people reporting having used heroin in the past year has remained fairly stable over the past five years, while the number of people reporting past-year non-medical use of pharmaceutical opioids has declined in each of the past three years.

Among those who reported past-year non-medical use of pharmaceutical opioids in 2018, hydrocodone remained the predominant pharmaceutical opioid used, whereas about 2 per cent had misused fentanyl products (diverted from legal sources). The results of the National Survey on Drug Use and Health suggest that the demand for fentanyl by itself remains low among those using opioids. Nevertheless, given that the survey excludes the institutionalized and the homeless populations, which may have disproportionately higher rates of non-medical use of opioids, these estimates are probably an underestimate of the true extent of such use in the United States. Nevertheless, such a large discrepancy

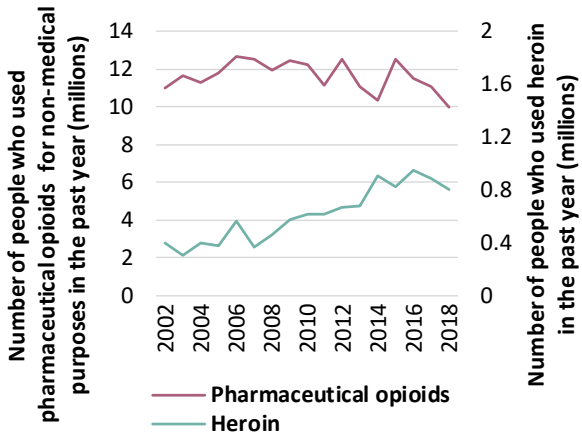
92 Bryce Pardo and others, "The synthetic opioid surge in the United States: insights from mortality and seizure data", document No. RR-3116-RC (Santa Monica, California, RAND Corporation, 7 November 2019).

FIG. 33 Trends in non-medical use of opioids and opioid overdose deaths in the United States, 2002–2018



Sources: United States, Substance Abuse and Mental Health Services Administration, *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health* (Rockville, Maryland, 2019); United States, Centers for Disease Control and Prevention, National Center on Health Statistics, "Provisional drug overdose death counts".

FIG. 34 Trends in use of heroin and non-medical use of pharmaceutical opioids, United States, 2002–2018

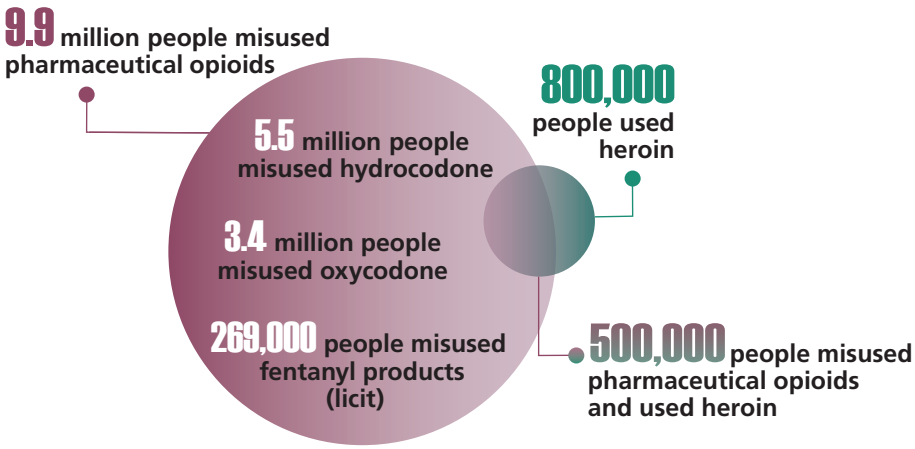


Source: United States, Substance Abuse and Mental Health Services Administration, *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health*.

in the trend between opioid overdoses and non-medical use of opioids suggests that the opioid crisis has increased the harms associated with opioid use rather than the number of people who use them.

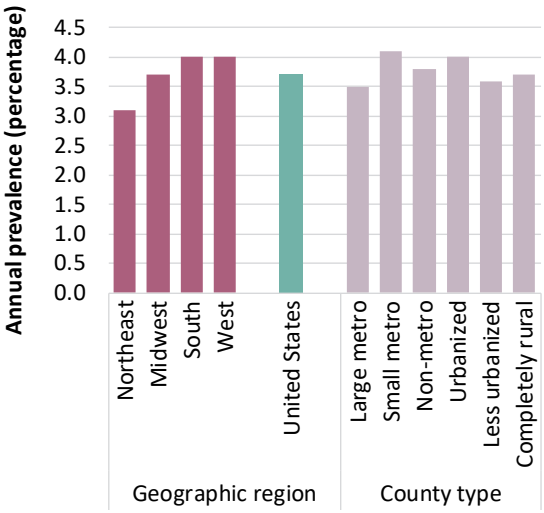
In 2018, approximately 10.3 million people (3.7 per cent of the population aged 12 years or older) had misused opioids in the past year in the United States. Most of them, 9.9 million (3.6 per cent of the population aged 12 years and older), reported non-medical use of pharmaceutical opioids, while almost 800,000 reported past-year use of heroin (comprising just 8 per cent of the total population who reported past-year misuse of opioids).

FIG. 35 Past-year misuse of pharmaceutical opioids and heroin in the United States, 2018



Source: United States, Substance Abuse and Mental Health Services Administration, *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health*.

FIG. 36 Opioids use, by geographical region and type of county, United States, 2018



Source: United States, Substance Abuse and Mental Health Services Administration, *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.*

What has driven the fentanyl crisis that began in 2013?

The unprecedented dynamic that has emerged in the United States is the persistence of fentanyls in the market from 2013 onwards. Local outbreaks of fentanyl use occurred in the United States and in countries in Europe, such as Bulgaria and Slovakia,[93] prior to 2013, but they all subsided, except in the case of Estonia (see section below). There were four localized outbreaks of fentanyl use and associated drug overdoses in the United States that could be linked, in each case, with a single supply source.[94] Those outbreaks remained limited, and once the source of fentanyl had been neutralized, the outbreak subsided. The last localized fentanyl outbreak occurred between 2005 and 2007 in Chicago, Detroit and Philadelphia, resulting in about 1,000 overdose deaths. The analyses of the samples tested showed that fentanyl (characterized as non-pharmaceutical fentanyl that was not diverted from licit sources) was mixed with either heroin or cocaine and sold through local illicit distribution channels.[95] The source of illicit fentanyl was identified to have been linked to a Mexican drug trafficking organization, and once the source was neutralized, the outbreak subsided.[96]

It is still not fully understood as to why the fentanyl outbreak in 2013 did not rapidly diminish as had happened in the past. The analysis of past outbreaks in the United States and the recent example in Sweden, suggest that the early identification and detection of the one supplier, or few suppliers, that introduced the fentanyls into the market quickly halted or reversed the spread of the substances in the market. Otherwise, as in the case of Estonia, once a market for fentanyls has been established, it tends to persist.

All factors driving fentanyl use converged from 2013 onwards in the United States and Canada, which may explain the unprecedented spread of the fentanyls in those markets: factors such as the diffusion of simpler, more effective methods of manufacture of synthetic opioids and their analogues (primarily fentanyls), assisted by the availability on the Internet of instructions for their manufacture; a shift from preparation by a limited number of skilled chemists to preparation by basic "cooks" who could simply follow the posted instructions; the discovery of ever more fentanyl analogues; a lack of effective control of precursors and oversight of the industry; expanding distribution networks that reduced the risk of detection through the use of postal services and the Internet; and increased licit trade including e-commerce.[97]

There is a great incentive for trafficking organizations to expand the fentanyl market: the large associated revenues. Compared with heroin, the production costs of single-dose fentanyls are substantially lower. For instance, it may cost between $1,400 and $3,500 to synthesize 1 kg of fentanyl, which could bring a return of between $1 million and $1.5 million from street sales.[98] For comparison, 1 kg of heroin purchased from Colombia may

93 Pardo and others, *The Future of Fentanyl and other Synthetic Opioids.*

94 These outbreaks were in California (1979–1988); Pennsylvania, one county (1988); Boston and New York (1992–1993) and Chicago, Detroit and Philadelphia (2005–2007).

98 Scott Stewart, "The fentanyl epidemic will spread far beyond America's shores", *Stratfor*, 16 July 2018.

TABLE 1 Characterization of past and current fentanyl crises in the United States

	Prior outbreaks	Current fentanyl crisis
Location	Generally localized	Not localized, although there are regional variations
Duration	Short	Nearly six years
Chemicals	Fewer fentanyl analogues (or potent analogues such as carfentanil)	Fentanyl dominates, but there are many and more potent analogues
Source	Mostly laboratories within the United States except in one case	Almost all imported, mostly from China and Mexico
Distribution	Limited; in two outbreaks traditional illicit market actors were involved	More widespread; both traditional illicit market actors and mail order or internet
Sold as…	Often sold as heroin, and in some cases appeared in cocaine	Heroin and pharmaceutical opioids, but an increasing share of cases of cocaine and psychostimulant overdose mention synthetic opioids

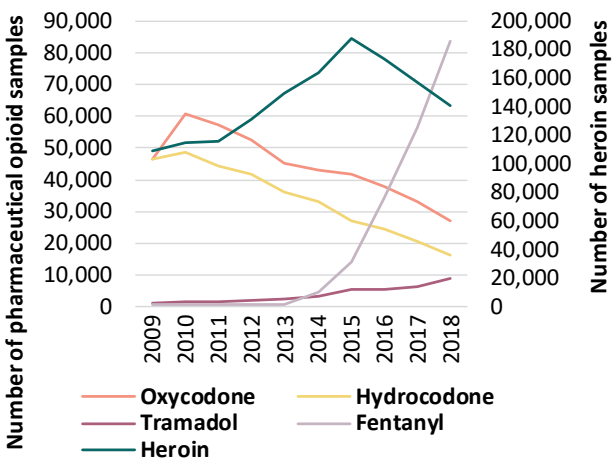
Source: Pardo and others, *The Future of Fentanyl and other Synthetic Opioids.*

cost $5,000 to $7,000,[99] around $53,000 at the wholesale level in the United States and around $400,000 at the retail level in the United States.[100] With fentanyls, the logistics for supply are also more flexible because fentanyls can be manufactured anywhere and are not subject to the climatic conditions or the vulnerable conditions required for the large-scale cultivation of opium poppy.

The current crisis of fentanyls appears to be more supply-driven than earlier waves of increases in the use of pharmaceutical opioids or heroin. Fentanyls are being used as an adulterant of heroin, are used to make falsified pharmaceutical opioids, such as falsified oxycodone and hydrocodone – and even falsified benzodiazepines – which are sold to a large and unsuspecting population of users of opioids and other drugs; users are not seeking fentanyl as such.[101, 102]

It seems that some local distributors are not able to distinguish between heroin, fentanyl and fentanyl-laced heroin, nor between diverted pharmaceutical opioids and falsified opioids containing fentanyl.[103] A general problem with fentanyls is dosing by non-professional "pharmacists", where small mistakes can lead to lethal results. Furthermore, as the overdose death data suggest, even people using cocaine and psychostimulants, such as methamphetamine, are also exposed – probably unintentionally – to fentanyls or other potent synthetic opioids mixed with those substances.

FIG. 37 Substances submitted to and analysed by forensic laboratories, by type of drug identified, United States, 2009–2018



Source: United States, Department of Justice, DEA, National Forensic Laboratory Information System, reports for different years.

99 United States, Department of Justice, DEA, *2017 National Drug Threat Assessment* (October 2017).

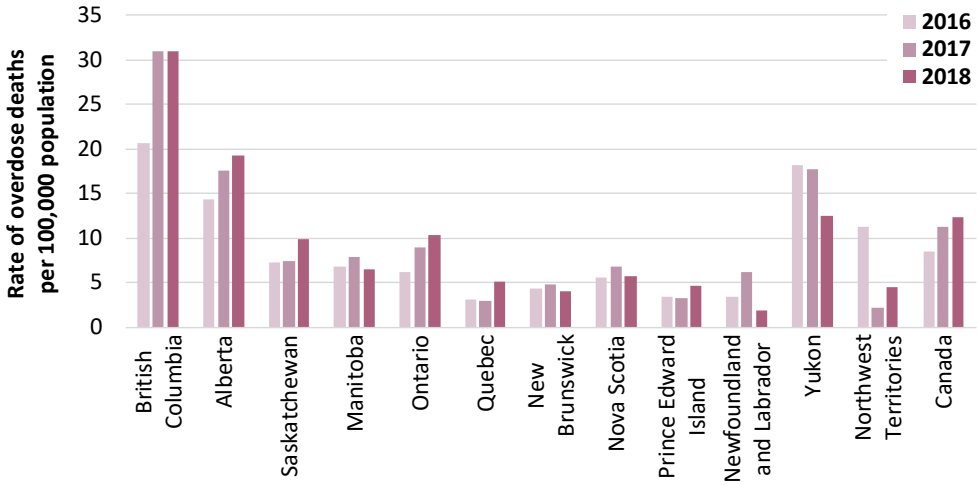
100 UNODC, heroin retail and wholesale prices in the United States, 2018, elaborated by the Office of National Drug Control Policy and reported in the annual report questionnaire for 2019.

101 Patil Armenian and others, "Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review", *Neuropharmacology*, vol. 134, part A (May 2018), pp. 121–132.

102 United States, Department of Justice, DEA, *2018 National Drug Threat Assessment.*

103 Ibid.

FIG. 38 Opioid overdose deaths in Canada, by province and territory, 2016–2018



Source: Canada, Public Health Agency, Special Advisory Committee on the Epidemic of Opioid Overdoses, "National report: apparent opioid-related deaths in Canada (January 2016 to March 2019)", September 2019.

Developments in Canada

In Canada, the opioid crisis is driven by the use of pharmaceutical opioids, both those diverted from licit channels and those originating in the illicit market, and an increasing number of opioid overdose deaths have been attributed to fentanyls since 2016.[104, 105] In Canada, the per capita consumption of opioids, such as hydromorphone and oxycodone, is the second highest in the world, after the United States.[106] In 2017, an estimated 12 per cent of the Canadian population aged 15 or older (3.5 million people) had used pharmaceutical opioids in the past year, of whom around 2 per cent reported non-medical use of pharmaceutical opioids.[107]

The number of opioid overdose deaths in Canada has increased by 50 per cent in the past three years, from 3,023 deaths (8.4 deaths per 100,000 population) in 2016 to 4,398 deaths (11.9 deaths per 100,000 population) in 2018. The majority (75 per cent) of overdose deaths are of young men. Overall, 26 per cent of total overdose deaths in 2018 were among those aged 30–39.[108] Various studies suggest that men are more likely than women to consume drugs alone, which puts them at risk of not receiving emergency assistance if they experience an overdose or other health complications.[109]

The geographical spread of overdose deaths is also uneven in Canada. In contrast to the United States, however, where north-eastern states are those most affected by the misuse of fentanyls and related overdose deaths, the concentration in Canada is mostly in the western parts of the country: British Columbia (31.2 overdose deaths per 100,000 population), Alberta (19.7 overdose deaths per 100,000 population) and Yukon in the north (12.3 deaths per 100,000 population). Those two provinces and territory in Canada have experienced the highest burden with regard to opioid overdose deaths.

About 80 per cent of the overdose deaths in Canada involved fentanyl or its analogues, although three out of four overdose deaths also involved non-opioid

Factors contributing to the fentanyl crisis in the United States

A number of factors have contributed to the current fentanyl crisis in the United States – factors that could be having an effect in other countries and regions. Over the past decade, there has been a rediscovery and proliferation of fentanyl and its analogues, as well as other research opioids such as U-47700, and a rediscovery of the relative ease with which these opioids can be synthesized.[a] The appearance of fentanyl and other research opioids seems to be supply-driven because – although they are serving an existing population of opioid users – most users do not seem to be actively seeking those substances.[b] These substances have either displaced a previously used opioid or filled a supply gap – as in the case of Estonia and Finland – but, overall, did not lead to a notable increase in the size of the opioid-using population.

The comparatively low cost of synthesizing opioids and the potential profit margin are a further incentive for drug trafficking organizations. The high potency of fentanyl and its analogues makes it convenient to synthesize and smuggle small amounts with relative ease. Trafficking 1 kg of fentanyl would be the equivalent of smuggling 50 kg of heroin, as 5 g of fentanyl is the equivalent to 150-250 g of heroin in terms of morphine-equivalent doses; 5 g of fentanyl is considered to be a wholesale quantity because it can serve a large number of users but it can be easily mailed in a small envelope.[c, d] Other technological advances such as the growth in e-commerce and sales of chemicals, among other goods sold, over the Internet, the darknet and use of alternative currencies such as bitcoin offer people with a computer and an Internet connection the possibility of maintaining their privacy while making transactions for those items with a perception of anonymity and safety. Given that only a small quantity of fentanyls are needed, mail orders and the use of small packages sent through postal services are another factor that has facilitated the spread of fentanyls in the United States and other markets. Finally, the relatively lax or poor regulations relating to the industrial manufacture of pharmaceutical, chemical and chemical precursors in some countries may have contributed to the proliferation and spread of synthetic opioids in the United States and other regions.[e]

[a] Pardo and others, *The Future of Fentanyl and other Synthetic Opioids.*

[b] Ibid.

[c] Stewart, "The fentanyl epidemic will spread far beyond America's shores".

[d] Pardo and others, *The Future of Fentanyl and other Synthetic Opioids.*

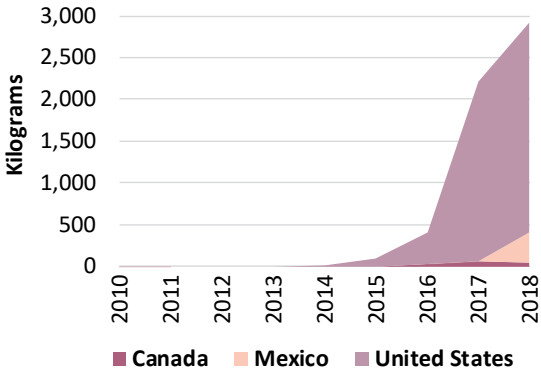
[e] Ibid.

substances. Between January 2012 and September 2017, 50 per cent of heroin samples analysed in Canada contained fentanyl or its analogues – carfentanil, furanylfentanyl and acetylfentanyl – while 2 per cent each of cocaine and methamphetamine samples also contained fentanyls.[110]

Trafficking of fentanyls into and across North America

Together with rapid increases in overdose deaths, the opioid crisis in North America was also characterized by rapidly rising seizures of fentanyls over the period 2010–2018, notably since 2014. Fentanyls are the most seized synthetic opioids in North America. Nonetheless, the upward trend in 2018 was far less pronounced than in previous years. Quantities of fentanyl seized in the United States continued to increase in 2018, although at a clearly slower pace than in previous years (showing a 32 per cent increase in 2018 following a fourfold increase in 2016 and a sixfold increase in 2017). Seizures of fentanyl increased in Mexico, but they declined by 36 per cent in Canada in 2018 after a

FIG. 39 Quantities of fentanyl seized in North America, 2010–2018



Source: UNODC, responses to the annual report questionnaire.

74 per cent increase in 2017.[111] In the same year, 32 NPS, including two fentanyl analogues, were scheduled by Chinese authorities, which brought the total number of controlled fentanyl analogues in that country to 25 in 2018.[112]

According to United States authorities, most of the fentanyls destined for the North American market have been manufactured in China in recent years, from where they were either shipped directly to the United States, mostly through postal services, or were first shipped to Mexico and, to a lesser extent, Canada and then smuggled into the United States.[113]

However, after the introduction by China in May 2019 of drug controls based on generic legislation with regard to the fentanyls, which effectively brought more than 1,400 known fentanyl analogues under national control in China,[114] early signs suggest that fewer fentanyls were smuggled from China to North America. At the same time, attempts to manufacture fentanyl and its analogues inside North America are increasing, notably in Mexico, by means of a method using precursor chemicals smuggled into the subregion from East Asia and South Asia.[115]

There has, in fact, been some manufacture of fentanyls in North America for some time. The United States reported one clandestine fentanyl laboratory dismantled in 2013, three in 2015 and nine in 2018, and the clandestine manufacture of fentanyl was the only type of clandestine manufacture of synthetic drugs on United States soil reported to have increased in 2018. Canada reported one fentanyl laboratory dismantled in 2012, one in 2016, one in 2017 and two in 2018.[116]

In Mexico, authorities seized a fentanyl laboratory in Culiacán, the state capital of Sinaloa,[117] in November 2017, and in September 2018 counter-narcotics authorities seized a laboratory in Baja California, Mexico, manufacturing fentanyl and carfentanil,[118] arresting two suspected associates of the Sinaloa Cartel. The laboratory was producing falsified tablets that were shipped to the north-eastern United States for sale. Moreover, in December 2018, the Office of the Attorney General of Mexico reported the dismantlement of a clandestine fentanyl laboratory in Mexico City.[119] In April 2019, the Mexican authorities reported the dismantling of a fentanyl laboratory in Culiacán.[120] The authorities seized some 33,000 fentanyl tablets as well as five containers containing heroin.[121] In June 2019, the authorities reported the dismantling of a clandestine laboratory in Nuevo León involved in the manufacture of chemical precursors for the manufacture of fentanyl, and which was possibly also manufacturing fentanyl.[122] Most of the larger Mexican drug

111 UNODC, responses to the annual report questionnaire.

112 United States, Department of Justice, Bureau for International Narcotics and Law Enforcement Affairs, *International Narcotics Control Strategy Report, vol. I, Drug and Chemical Control* (Washington D.C., March 2019).

113 United States, Department of Justice, DEA, *2018 National Drug Threat Assessment 2018.*

114 E/INCB/2019/1.

115 INCB, "Experts and industry strategize next steps in implementing INCB's list of fentanyl-related substances with no legitimate uses", 4 September 2019.

116 UNODC, responses to the annual report questionnaire.

117 Steven Dudley and others, "Mexico's role in the deadly rise of fentanyl" (Washington D. C., Wilson Center Mexico Institute, 2019).

118 Bureau for International Narcotics and Law Enforcement Affairs, *International Narcotics Control Strategy Report*, vol. I.

119 Dudley and others, "Mexico's role in the deadly rise of fentanyl".

120 Mexico, Sinaloa, Secretaría de Seguridad Pública, "Comunicación SSPE/141/2019: Policía Estatal Preventiva y Fuerzas Armadas aseguran presumiblemente el primer laboratorio de fentanilo a nivel nacional".

121 Mexico, Fiscalía General de la República, "Comunicado FGR 183/19: FGR asegura en Sinaloa más de 33 mil pastillas de fentanilo, heroína y ácido clorhídrico", 17 April 2019.

122 Mexico, Fiscalía General de la República, "Comunicado FGR 294/19: FGR asegura en Nuevo León laboratorio posiblemente utilizado para elaborar fentanilo", 16 June 2019.

trafficking groups are already involved in the trafficking of fentanyls from Mexico to the United States, most notably the Sinaola Cartel and the Jalisco New Generation Cartel.[123]

The clandestine manufacture of fentanyls within North America is thus not really a new phenomenon and has the potential to increase in importance following the recent control of fentanyls substances in China. Moreover, the clandestine manufacture of fentanyl has already spread beyond North America to neighbouring subregions, as a clandestine fentanyl laboratory was dismantled in the city of Santiago, Dominican Republic, in 2017.[124]

At the same time, there is a risk that other countries with a large and thriving pharmaceutical sector may become involved in the clandestine manufacture of fentanyls. In 2018, for example, authorities of India reported two relatively large seizures of fentanyl destined for North America.[125] Furthermore, according to United States authorities, in September 2018, the Directorate of Revenue Intelligence of India, in cooperation with DEA of the United States Department of Justice, dismantled the first known illicit fentanyl laboratory in India and seized approximately 11 kg of fentanyl.[126]

Opioids in Europe: are there indications of a fentanyl-led crisis?

In the European market, fentanyls have started to be detected in seizures and overdose deaths, and attempts to gain a share of the illicit opioid market with these drugs have been detected and suppressed in Sweden and the United Kingdom, for example. So far, there is no indication of an established market for fentanyls as an adulterant or as a main substance in Europe, with the exception of Estonia, where fentanyl has developed an isolated niche market since 2013. There are, however, signs of an increase in the medical use of opioids in Europe as seen in the prescription rates for opioids for pain management.

In Western and Central Europe, there are an estimated 1.3 million high-risk opioid users[127] (0.4 per cent of the population aged 15–64). Heroin remains the main opioid used in the subregion, with recent estimates in many countries suggesting an increase in the use of the drug, in a context in which its purity is reported as relatively high and its price relatively low. Over the past five years, there has also been an increase in drug overdose deaths, with 8 or 9 deaths of every 10 overdose deaths in the European Union involving heroin.[128]

The health-care and social needs of an ageing and increasingly vulnerable cohort of long-term opioid users continues to grow; and data on overdose deaths reflect the fact that older high-risk opioid users may be at the greatest risk of overdose death (the current average age of people dying of overdose is 39 years).[129]

There are also indications that other opioids such as methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone are being increasingly misused in the European Union. For instance, one of every five people entering drug treatment for an opioid-related problem in 2018 reported a synthetic opioid as their main problem drug instead of heroin.[130]

In the European Union, since 2012 more than 30 fentanyl analogues have been detected and reported.[131] These are available on the Internet, through the darknet and at street level. They are sold as heroin, other illicit opioids and cocaine but also as a substitute for pharmaceutical drugs such as

123 Dudley and others, "Mexico's role in the deadly rise of fentanyl".

124 *Report of the International Narcotics Board for 2018* (E/INCB/2018/1).

125 Bryce Pardo, "Illicit supply of fentanyl and other synthetic opioids: transitioning markets and evolving challenges", RAND Corporation Testimony Series (Santa Monica, California, RAND Corporation, 25 July 2019).

126 Bureau for International Narcotics and Law Enforcement Affairs, *International Narcotics Control Strategy Report*, vol. I.

127 As defined by EMCCDA, high-risk opioid use is the recurrent use of opioids or other drugs that is causing actual harms (negative consequences, including dependence, but also other health, psychological or social problems) to the person, or is placing the person at a high probability/risk of suffering such harms.

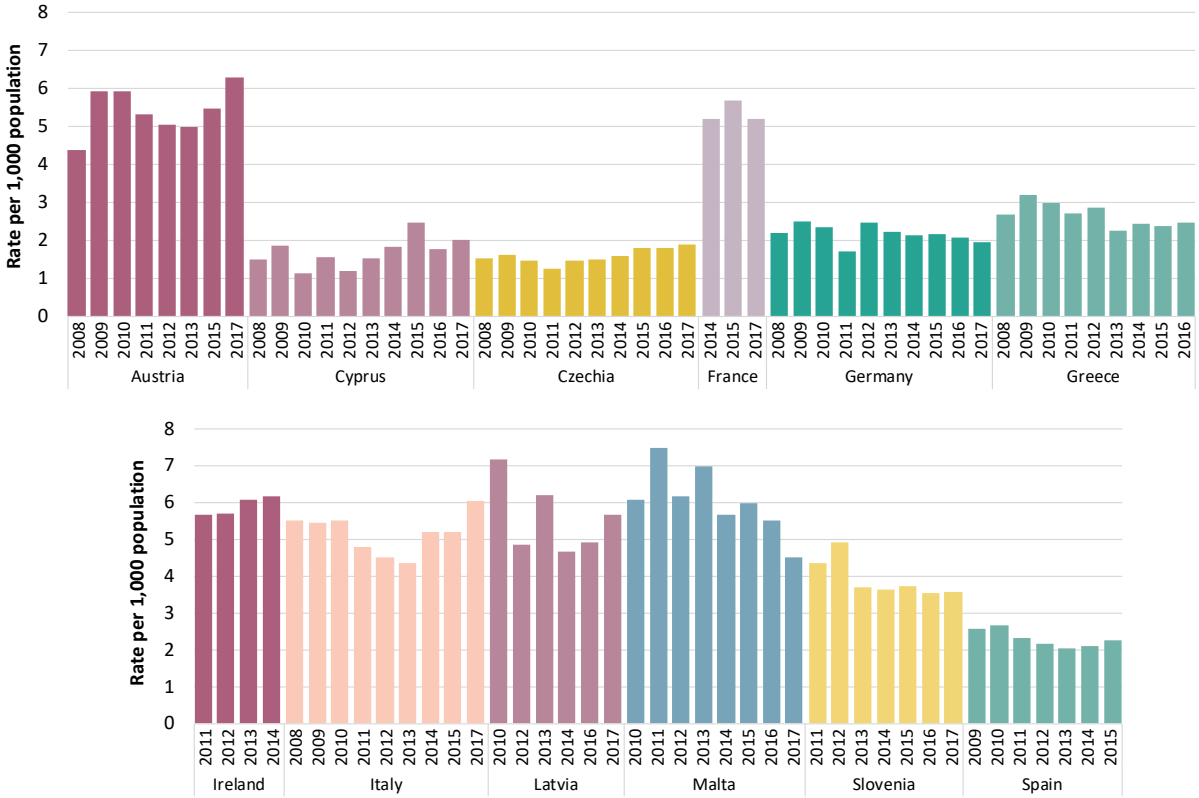
128 EMCCDA, *European Drug Report 2019: Trends and Developments* (Luxembourg, Publications Office of the European Union, 2019).

129 Ibid.

130 Ibid.

131 Ibid.

FIG. 40 Trends in high-risk opioid use in countries in Western and Central Europe



Source: EMCDDA, Statistical Bulletin 2019.

Note: High-risk opioid use is defined by EMCDDA as recurrent drug (opioid) use that causes actual harms (negative consequences) to the person (including dependence, but also other health, psychological and social problems) or places the person at a high probability/risk of suffering such harms.

Xanax.[132] Although the total number of fentanyl-related overdose deaths in Europe is not available, the number of deaths remains much lower in Europe than in North America. In the European Union, over 2017 and 2018, the fentanyl analogue cyclopropylfentanyl was involved in 78 deaths, carfentanil in 61 deaths and acryloylfentanyl in 47 deaths.[133] However, while outbreaks of deaths related to fentanyl and its analogues have been reported in many countries, their number is probably underestimated in Europe. Moreover, despite the threat, the current capacity to detect and report on the availability, use and consequences of synthetic opioids appears to remain limited in the European Union.[134] Nevertheless, there are developments in different European countries that are worth observing.

In Norway, there has been a shift in the relative importance of heroin, as just 20 per cent of overdose deaths in 2017 were attributed to heroin, which is significantly below the figure for 2006, when approximately half of overdose deaths were attributed to the drug. Methadone, buprenorphine and fentanyls are identified as the main substances involved in overdose deaths in Norway.[135]

In England, post-mortem reports and drug seizures in the second quarter of 2017 suggested that fentanyl and its analogues had been introduced into the heroin supply in the north of the country. Law enforcement authorities dismantled a laboratory that may have been the site where the mixing of

132 Ibid.

133 Ibid.

134 Ibid.

135 Ibid.

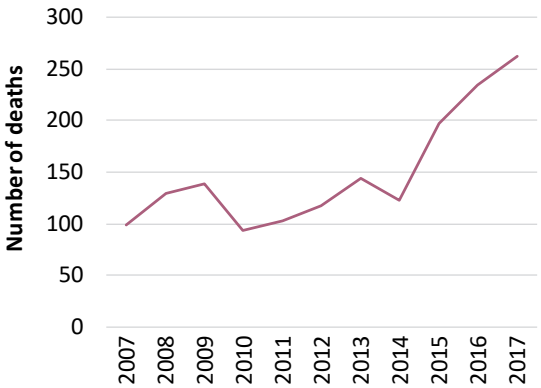
fentanyls with heroin was taking place. Investigations suggested that some 26 fentanyl-related deaths in urban areas of northern England could be linked with that laboratory. There were an additional five cases in the north-east and three cases in other regions of the country.[136] In 2017, however, there were a total of 75 fentanyl-related deaths recorded in the United Kingdom. There are signs of attempts to introduce fentanyls in the United Kingdom opioids market, but so far these attempts appear sporadic, geographically limited or linked to a single source of supply. Effective monitoring of the emergence of fentanyl-related deaths in Europe requires further investigation and detection of the multiple substances that may be involved in drug-related deaths.

Increasing rates of opioid prescriptions show different outcomes in the non-medical use of the drugs and in overdose deaths in Germany and the Netherlands

While the illicit opioid market is diversifying, heroin remains the main opioid used for non-medical purposes among opioids users in most European countries, but the medical use of opioids is substantially increasing.

At the global level, Germany was the second largest consumer of opioid pain relievers, with an estimated 28,862 S-DDD per million population per day for medical use in 2017, followed by Austria, Belgium and Switzerland.[137] In Germany, the number of pharmaceutical opioids overall and the number of people receiving opioid treatment have increased over the past few decades;[138] in most instances, prescriptions were given for non-chronic cancer pain.[139] A review of scientific literature from Germany published between 1985 and 2016 showed that out of the 12 studies reviewed, 6 studies reported a prevalence for patients with medical use of any opioid[140]

FIG. 41 Trend in overdose deaths in the Netherlands, 2007–2017



Source: EMCDDA, Statistical Bulletin 2019.

for long-term treatment of non-cancer chronic pain ranging from 0.54 to 5.7 per cent, while four studies reported a prevalence for patients with medical use of opioids at 0.057 to 1.39 per cent of the population.

With respect to heroin users and non-medical users of opioids in Germany, the extent of high-risk opioid use has remained stable over the past decade. In 2016, it was estimated that 3.05–3.11 persons per 1,000 population aged 15–64 were engaged in high-risk opioid use (between 164,794 and 167,794 people),[141] while the number of overdose deaths – the majority attributed to opioids – has declined in Germany. In 2018, 629 overdose deaths – half of the total number of overdose deaths in Germany – were attributed to opioids (heroin and other opioids) alone or in combination with other drugs, and 53 deaths were attributed to fentanyls (compared with 110 deaths in 2017).[142] Furthermore, data show that in Germany there were more deaths related to fentanyl than to fentanyl analogues. In 2018, the authorities reported 25 cases of poisoning deaths linked to fentanyl only, and five cases linked to fentanyl analogues only. Similarly, in cases of

136 Ibid.

137 *Narcotic Drugs: Estimated World Requirements for 2019–Statistics for 2017* (E/INCB/2018/2), p. 250.

138 Bastian Rosner and others, "Opioid prescription patterns in Germany and the global opioid epidemic: systematic review of available evidence", *PLoS ONE*, vol. 14, No. 8 (August 2019).

139 Ibid.

140 This reflects the proportion of population who had a prescription for opioids for long-term opioid treatment, for chronic non-cancer pain.

141 Ludwig Kraus and others, "Estimation of the number of people with opioid addiction in Germany", *Deutsches Ärzteblatt International*, vol. 116, No. 9 (March 2019), pp. 137–143.

142 Germany, Bundeskriminalamt, "Rauschgiftkriminalität: Bundeslagebild 2018" (September 2019).

drug-related deaths caused by multiple opioids, there were 28 deaths that involved fentanyl and only one case involving a fentanyl analogue.[143] It is interesting to note that the decline in fentanyl-related deaths in 2018 was more pronounced for fentanyl analogues than for fentanyl as such.

In the Netherlands, a retrospective multi-source database study reported that between 2008 and 2017, the overall number of medical users of opioids nearly doubled, from 4,109 per 100,000 population to 7,489 per 100,000 population over the 10-year period.[144] The main increase was attributed to the number of oxycodone users, which quadrupled from 574 to 2,568 per 100,000 population in the same period.

The negative consequences of opioid use also seem to have increased in the Netherlands, although this may be a combination of medical and non-medical use. The number of opioid-related hospital admissions tripled from 2.5 to 7.8 per 100,000 inhabitants, and between 2008 and 2015 the number of people in drug treatment for opioid use disorders other than heroin also increased, from 3.1 to 5.6 per 100,000 population. Drug overdose deaths attributed to opioids, which had remained stable between 2008 and 2014 at 0.21 deaths per 100,000 population, increased thereafter to 0.65 per 100,000 population in 2017. This increase in opioid overdose deaths is attributed to the increase in overdose deaths involving pharmaceutical opioids, which had remained stable earlier (in the period 2008–2014), at an average of 0.091 deaths per 100,000 (15 cases) and increased to 0.49 deaths per 100,000 (83 people) in 2017. By contrast, overdose deaths attributed to heroin, methadone and opium remained stable in the period 2008–2017.

Sweden and Estonia show a decline in fentanyl-related overdose deaths

In Sweden, the overall opioid market was dominated by heroin until 2014. In 2006, diverted fentanyl patches appeared in the drug market and stayed, although their market share remained relatively limited.[145] Fentanyl analogues were introduced into the drug market in Sweden in 2014, through online sales of fentanyl analogues, mainly in the form of nasal sprays but also tablets, powder and capsules.[146]

Although the quantities of fentanyls seized in Sweden did not decline in 2018 (they actually rose marginally, from 4.4 kg in 2017 to 4.6 kg in 2018),[147] the overall threat emerging from fentanyls was considered to have declined in 2018, following the dismantling of the country's main distribution network. According to Swedish authorities, that network was mainly selling nasal sprays containing fentanyl analogues that originated in China, sold through the Internet to customers in Sweden. This led, mainly due to problems with correct dosing, to a significant number of fentanyls overdose deaths in Sweden in recent years.[148]

Sweden generally reports one of the highest overdose rates in Europe and has experienced overdose deaths attributed to the use of opioids, including heroin, fentanyl and fentanyl analogues. A total of 539 overdose deaths were reported in 2017 (9.5 per 100,000 population), of which opioids accounted for over 90 per cent. Since 2015, fentanyl analogues have resulted in an increasing number of overdose deaths. However, these overdose deaths declined considerably in 2018, in line with the dismantling of the main fentanyl distribution network, with only 18 deaths attributed to fentanyl and 11 attributed to fentanyl analogues; however, the majority of those deaths involved more than one substance.[149] Overall, most fentanyl analogue deaths in 2017 and 2018 were attributed to cyclopropylfentanyl, while in 2018 four deaths were attributed to methoxyacetylfentanyl as well. In 2018, people who died from a fentanyl overdose were older on average (median age of 44.6 years) than those whose overdose was

143 Ibid.

144 Gerard Arnoldus Kalkman and others, "Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study", *Lancet Public Health*, vol. 4, No. 10 (August 2019).

145 Pardo and others, *The Future of Fentanyl and other Synthetic Opioids.*

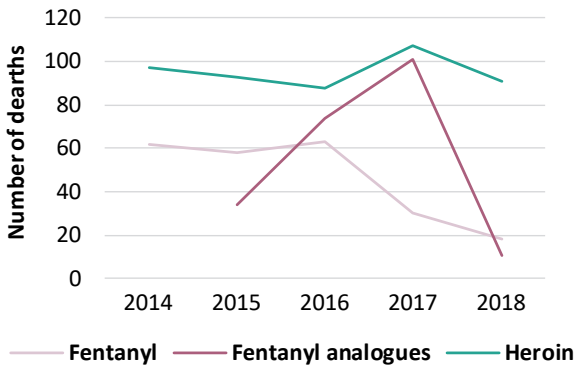
146 Swedish Police Authority, National Operations Department, "Swedish National Threat Assessment on fentanyl analogues and other synthetic opioids" (October 2018).

147 UNODC, responses to the annual report questionnaire.

148 For a more in-depth analysis of the Swedish market for fentanyl and its analogues, see Swedish Police Authority, "Swedish National Threat Assessment on fentanyl analogues and other synthetic opioids".

149 Ibid.

FIG. 42 Trends in opioid overdose deaths in Sweden, 2014–2018



Source: Sweden, National Board of Forensic Medicine, 2019.

caused by fentanyl analogues (median age of 32.9 years).[150, 151]

Estonia and Finland are two countries where two synthetic opioids, fentanyl (in the case of Estonia) and buprenorphine (in the case of Finland), completely replaced heroin and established themselves in the opioid market). In Finland, after the heroin shortage and disruption of the heroin market beginning in 2001, the proportion of clients entering treatment for non-medical use of buprenorphine increased from 3 per cent in 1998 to more than one third in 2008[152] and as of 2018 accounted for almost all opioid users in treatment.[153] There are an estimated 13,800 high-risk drug users in Finland and quite common among them is the concurrent use of amphetamines and opioids.[154] In 2018, there were 200 drug overdose cases registered, a slight increase compared with 2016 (194 deaths). Toxicological data indicate that buprenorphine, in combination with alcohol or benzodiazepines, was involved in the majority of drug overdose cases in Finland.[155]

150 Sweden, National Board of Forensic Medicine.

151 EMCDDA, *Drug-related Deaths and Mortality in Europe.*

152 Hanna Uosukainen and others, "Twelve-year trend in treatment seeking for buprenorphine abuse in Finland", *Drug and Alcohol Dependence*, vol. 127, Nos. 1–3 (January 2013), pp. 207–214.

153 EMCDDA, "Finland: Finland drug report 2018" (Helsinki, June 2018).

154 EMCDDA, "Finland: Finland country drug report 2019" (Helsinki, June 2019).

155 Ibid.

Following a decline in heroin availability in Estonia, 3-methylfentanyl first appeared on the drug market in 2002. By 2005, 3-methylfentanyl and 3-methylfentanyl/fentanyl mixtures accounted for the majority of opioids seized and had replaced heroin use in the country.[156] Although national estimates of opioid use are not available for Estonia, the majority of people who inject drugs (estimated at about 8,600 people) in that country reportedly inject 3-methylfentanyl and, since 2015, other fentanyl analogues such as furanylfentanyl, acrylfentanyl, carfentanil and ocfentanil.[157]

Estonia has also recorded a high rate of opioid overdose deaths (13 deaths per 100,000 population) attributed to the use of fentanyls. After a peak in the number of opioid overdose deaths in 2012 (170 deaths), the rate decreased steadily until 2015 then increased in 2016 (114 deaths, or 13.4 deaths per 100,000 population) and declined again in 2017. The results of toxicological examinations attributed the majority of those deaths to synthetic opioids, mainly 3-methylfentanyl and other fentanyls such as carfetanyl, furanylfentanyl and acrylfentanyl.[158]

Trafficking of fentanyls in Europe

Overall seizures of fentanyls reported in Europe are still very small compared with those reported in North America, reflecting a far smaller market for the substances. While countries in North America reported overall seizures of fentanyl and its analogues of 5,396 kg in the period 2014–2018, seizures of those substances reported by countries in Europe totalled 138 kg in the same period, which is the equivalent of a mere 3 per cent of the amount of fentanyls seized in North America.

Nonetheless, the trafficking of fentanyls appears to be spreading in Europe as well, with a total of 15 European countries reporting seizures of fentanyls in the period 2014–2018, up from five countries in the period 2009–2013.

Most of the quantities of fentanyls seized in Europe in the period 2014–2018 were reported by countries

156 Ilkka Ojanperä and others, "An epidemic of fatal 3-methylfentanyl poisoning in Estonia", *International Journal of Legal Medicine*, vol. 122, No. 5 (September 2008), pp. 395–400.

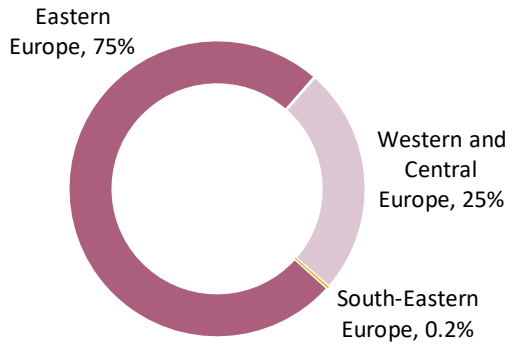
157 EMCDDA, "Estonia: Estonia drug report 2018" (June 2018).

158 Ibid.

FIG. 43 Trends in fentanyls overdose deaths in Estonia, 2008–2017

Source: EMCDDA, Statistical Bulletin 2019.

FIG. 44 Distribution of the quantity of fentanyls seized in Europe, by subregion, 2014–2018



Source: UNODC, responses to the annual report questionnaire.

Note: Distribution calculated on the based on a total of 138 kg of fentanyls seized over 2014–2018.

in Eastern Europe (103 kg), mainly reflecting the significant seizures of 3-methylfentanyl (98 kg) reported by the Russian Federation in 2015. Seizures reported by the Russian Federation accounted for over 99 per cent of all fentanyls seized in Eastern Europe in that five-year period, with seizures by Ukraine accounting for the remainder. In addition to 3-methylfentanyl and fentanyl, the Russian Federation also seized carfentanil, furanylfentanyl, crotonylfentanyl, acetylfentanyl and *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropionamide (benzylfentanyl) in 2018.[159]

In Western and Central Europe, the seizure of 34 kg of fentanyls was reported in the period 2014–2018. Most of it was fentanyl itself (92 per cent of all fentanyls seized), followed by carfentanil (1 per cent), fluranylfentanyl (0.8 per cent) and 3-methylfentanyl (0.3 per cent). In South-Eastern Europe, fentanyl was reported as being seized only by Bulgaria, in 2015 (0.3 kg).

However, seizures of pharmaceutical opioids, as a broad category, were more prominent and had a different distribution. An analysis of the reported broader categories of pharmaceutical opioids, other illicit opioids and non-specified opioids shows significant annual variations of a few hundred kilograms from 2009 until 2016, when totals for this reporting category increased to 3 tons, and later peaked at over 6 tons in 2017 before declining to just under 2 tons in 2018. At the same time, data indicate that in recent years, notably since the period 2016–2018, such seizures were dominated by opioid seizures reported in Western and Central Europe.

While the overall importance of fentanyls in the quantities of opioids seized and in the number of seizure cases in Europe has been modest to date, the situation is different with new opioids: around 70 per cent of the seizure cases of new opioids seized in the European Union in 2017 concerned fentanyl analogues. The most frequently seized new synthetic opioid in 2017 was carfentanil (318 cases), followed by furanylfentanyl (183 cases), cyclopropylfentanyl (131 cases) and ocfentanil (55 cases).[160]

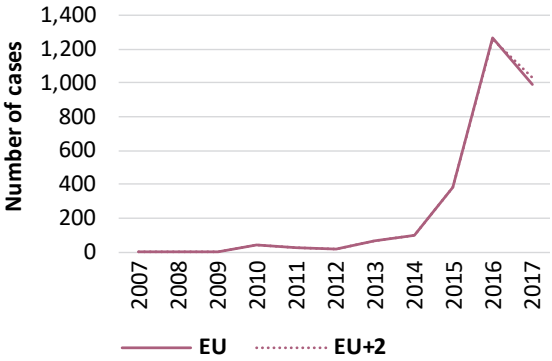
There have been much more erratic annual seizure patterns with respect to the quantities of fentanyls seized. While the overall trend in Western and Central Europe appears to show an increase, data for 2018 show a significant decline, which is possibly linked to the improved availability of heroin across Europe, in combination with improved controls of exports of fentanyls from China.[161]

159 Presentation given by the General Administration for Drug Control, Ministry of Internal Affairs of the Russian Federation, at the international conference on "Combating suspects dealing in drugs on the Internet: prosecution and prevention", organized by the Bavarian Landeskriminalamt and the Austrian Bundeskriminalamt, Landshut, Germany, 6–8 May 2019.

160 EMCDDA and Europol, *EU Drug Markets Report 2019* (Luxembourg, Publications Office of the European Union, 2019).

161 Ibid.

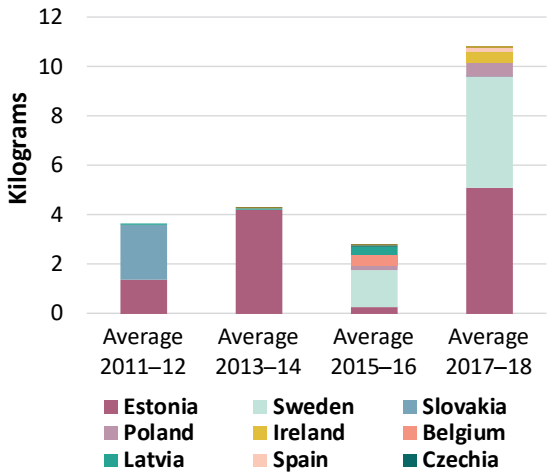
FIG. 45 Seizures of new opioids, European Union, 2007-2017



Source: EMCDDA and Europol, *EU Drug Markets Report 2019* (Luxembourg, Publications Office of the European Union, 2019).

Note: Seizures of new opioids reported to the EU Early Warning System (excluding tramadol); "EU" designates 28 European Union member States as at November 2018; "EU+2" designates 28 European Union member States plus Norway and Turkey.

FIG. 47 Quantities of fentanyl(s) seized in Western and Central Europe, 2011–2018



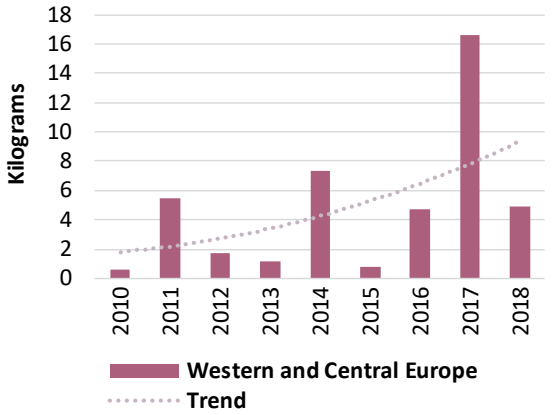
Source: UNODC, responses to the annual report questionnaire.

The main source country of the fentanyls detected in the countries of the European Union appears to be China.[162, 163] Most quantities are seized in Estonia and Sweden. Fentanyls are purchased throughout the European Union through online platforms on

162 UNODC, responses to the annual report questionnaire.

163 EMCDDA and Europol, *EU Drug Markets Report 2019*.

FIG. 46 Quantities of fentanyls seized in Western and Central Europe, 2010–2018



Source: UNODC, responses to the annual report questionnaire.

the surface web and the darknet.[164] However, most notable have been the shifts reported in recent years by Estonia: whereas fentanyl found on the market used to be sourced in the Russian Federation, as of 2017 new fentanyl analogues found on the market mainly originated in China and were mostly ordered online.[165] While Estonia reported record seizures of fentanyls to UNODC in 2017, seizures of fentanyl appear to have declined significantly in 2018. Estonia indicated difficulties faced by law enforcement in detecting small shipments of drugs arriving by postal services in the country.[166]

Non-medical use of tramadol: the other opioid crisis

Tramadol, a pharmaceutical opioid currently not controlled under international drug control conventions, has been used for the management of moderate to severe pain. Tramadol's potency is comparable to that of codeine but is only about 10 per cent the potency of morphine. It is also mentioned as an analgesic in the World Health Organization guidelines for cancer pain relief and is listed in several national essential medicines lists, most notably in low- and middle-income countries.[167] Nevertheless,

164 Ibid.

165 EMCDDA, "Estonia: Estonia country drug report 2019".

166 Ibid.

167 World Health Organization, "Critical review report: tramadol", Forty-first Meeting of the Expert Committee on Drug Dependence, Geneva, 12–16 November 2018.

in the past few years tramadol has increasingly been used for non-medical purposes and has raised public health concerns, in particular in West, Central and North Africa. The non-medical use of tramadol is also reported by many countries in the Middle East, West Asia, South and South-East Asia, Europe and North America.

Many young people and some categories of workers misuse tramadol to boost their energy, to be able to work long hours at physically demanding and tedious jobs, or for "sexual ecstasy and performance", perceived euphoria, attentiveness and self-medication, and to relieve pain.[168, 169] However, concerns about the non-medical use of tramadol have also arisen as there is an increasing number of people entering treatment for tramadol use disorders.

Non-medical use of tramadol remains a major public health concern in West, Central and North Africa

Many countries in West, Central and North Africa report the non-medical use of tramadol as one of the main threats in drug use, although quantitative information on the actual size of the population using tramadol non-medically is not available for most countries.

Nigeria, the only country in Africa to have conducted a population survey on drug use, shows the magnitude of the problem. In Nigeria, around 3 million men (6 per cent of the male population) and 1.6 million women (3.3 per cent of the female population) aged 15–64 reported the non-medical use of pharmaceutical opioids (mainly tramadol) in the past year in 2018.[170] (For comparison, the past–year prevalence of non-medical use of pharmaceutical opioids in the United States was 3.6 per cent, while that of tramadol was 0.5 per cent of the population aged 12 and older in 2018).[171] The prevalence of the non-medical use of pharmaceutical opioids in Nigeria was above the national average (which was 4.7 per cent) in the south-western (7.8 per cent) and the north-eastern (6.5 per cent) parts of the country. While there was no age group among which it was low, it was particularly high among people in the age brackets 35–39 and 60–64. One of every five persons reporting the non-medical use of pharmaceutical opioids was suffering from opioid-related disorders.

The drug use survey in Nigeria reveals tramadol to be a more accessible opioid than heroin, although it is still relatively costly if used frequently. While use of tramadol appears to cost about one third the price of heroin ($3.60 versus $10 per day of use in the past 30 days), in a country where the minimum wage of a full-time worker is around $57 per month, regular tramadol use still poses a considerable financial burden on users and their families.

There is no information on the prevalence of drug use in other West African countries, but treatment data reveal tramadol to be the main drug of concern for people with drug use disorders. Tramadol ranks highly among the substances for which people were treated in West Africa in the period 2014–2017. This was particularly the case in Benin, Mali, the Niger, Nigeria, Sierra Leone and Togo.[172]

The non-medical use of tramadol is of particular concern among young people in many countries in that subregion. For example, a cross-sectional study among 300 young people in western Ghana found that while the majority (85 per cent) of respondents knew someone who misused tramadol, more than half of the young people interviewed had used tramadol themselves for non-medical purposes, and one third of the users reported misusing 9–10 doses of tramadol per day.[173] Another qualitative study from Ghana reported curiosity, peer pressure and iatrogenic addiction as the three main factors for initiation and continuing non-medical use of

168 *World Drug Report 2019: Depressants*.

169 Yasna Rostam-Abadi and others, "Tramadol use and public health consequences in Iran: a systematic review and meta-analysis", *Addiction*, (March 2020). Available at https://doi.org/10.1111/add.15059.

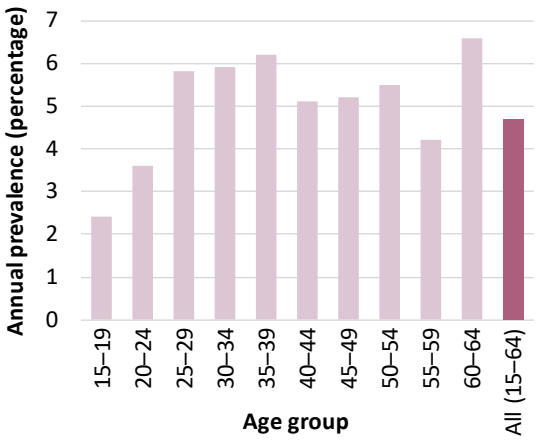
170 National Bureau of Statistics and UNODC, *Drug Use Survey in Nigeria 2018* (*Funded by the European Union)* (Vienna, 2019).

171 United States, Substance Abuse and Mental Health Services Administration, *Key Substance Use and Mental Health Indicators: Results from the 2018 National Survey on Drug Use and Health* (Rockville, Maryland, 2019).

172 UNODC, European Union and Economic Community of West African States, *West African Epidemiology Network on Drug Use (WENDU) Report: Statistics and Trends on Illicit Drug Use and Supply 2014–2017* (2019).

173 Erik Kwasi Elliason and others, "Abuse and misuse of tramadol among the youth in the Wassa Amenfi West Municipality in the western region of Ghana", *Psychology and Psychological Research International Journal*, vol. 3, No. 7 (September 2018).

FIG. 48 Non-medical use of pharmaceutical opioids (mainly tramadol) by age group, in Nigeria, 2018



Source: National Bureau of Statistics and UNODC, *Drug Use Survey in Nigeria 2018.*

tramadol, while perceived euphoria, attentiveness, relief from pain, physical energy and aphrodisiac effects were mentioned as some of the reasons for continuing non-medical use of tramadol.[174]

In North Africa, tramadol is reported as the main opioid used non-medically in Egypt, where scientific literature about tramadol misuse is more available than elsewhere in the subregion. An estimated 3 per cent of the adult population misused tramadol in 2016, the latest year for which data are available, while 2.2 per cent were diagnosed with tramadol dependence.[175] In drug treatment, tramadol was also the main drug, accounting for 68 per cent of all people treated for drug use disorders in 2017.[176]

A cross-sectional study conducted over the period 2012–2013 among 1,135 undergraduate college students in Egypt showed that 20.2 per cent of male and 2.4 per cent of female students had misused tramadol at least once during their lifetime, resulting in an overall lifetime prevalence of 12.3 per cent.

The average age of initiation of non-medical use of tramadol was around 17 years. Polydrug use was also quite common, with the majority of respondents (85 per cent) reporting use of either tobacco, alcohol or cannabis with tramadol. Among those who had misused tramadol, 30 per cent were assessed to be tramadol dependent.[177]

Another study in 2014 among patients in a psychiatric facility in Egypt showed that psychiatric disorders were substantially higher among those with an opioid use disorder related to tramadol than among those who did not have opioid use disorder (49 per cent versus 24 per cent). Among those with tramadol use disorder, most had borderline personality disorders and anxiety disorders, suggesting that people with tramadol use disorder are also likely to have a high prevalence of psychiatric comorbidity.[178]

Similarly, another study reported that cannabis and tramadol were the two most prevalent substances among patients presenting with first-episode drug-induced psychosis in a psychiatric facility in Egypt.[179] The authors concluded, however, that the prevalence of cannabis use and non-medical use of tramadol among those presenting with drug-induced psychosis might be related to environmental and economic factors, in which the most available substances are the most frequently encountered, and that drug preference is related to a larger extent to drug availability rather than an individual liking of the substance used or misused.

In the Sudan, while population-based estimates of the extent of substance use are not available, research suggests that the drug scene has rapidly changed, especially with the increasing non-medical use of pharmaceutical drugs among young people, including tramadol, benzodiazepines, cough syrups and

174 Abdul-Ganiyu Fuseini and others, "Facilitators to the continuous abuse of tramadol among the youth: a qualitative study in northern Ghana", *Nursing Open,* vol. 6, No.4 (October 2019), pp. 1388–1398.

175 Egypt, General Secretariat of Mental Health of the Ministry of Health, "Report of the General Secretariat of Mental Health and Addiction Treatment on tramadol" (2017).

176 Ibid.

177 Medhat Bassiony and others, "Opioid use disorders attributed to tramadol among Egyptian university students", *Journal of Addiction Medicine*, vol. 12, No. 2 (March/April 2018), pp. 150–155.

178 Medhat Bassiony and others, "Psychiatric comorbidity among Egyptian patients with opioid use disorders attributed to tramadol", *Journal of Addiction Medicine*, vol. 10, No. 4, (July/August 2016), pp. 262–268.

179 Taha and others, "Cannabis and tramadol are prevalent among the first episode drug-induced psychosis in the Egyptian population", p. 16.

antihistamines, trihexyphenidyl, anticonvulsants and neuropathic pain agents such as pregabalin and gabapentin.[180]

Context of lack of access to opioid pain medication under international control in many countries where tramadol is used

The trafficking and availability of tramadol for its non-medical use is a public health concern, but limited distribution of tramadol for medical use would also pose a public health concern, in particular in Africa, where there is a chronic shortage of pain medications. There are no data on the availability and use of tramadol for medical purposes, but data on internationally controlled substances clearly highlight the gaps in the accessibility of pain medications. The general lack of access to opioid-related pain medications under international control is a specific problem for developing countries, which is even more pronounced in countries in West and Central Africa than in other parts of the world.

INCB data show that the licit use of internationally controlled opioids amounted to just 174 S-DDD per million inhabitants per day in Africa in the period 2015–2017, much lower than in other regions and subregions (for comparison, Asia: 317 S-DDD per million inhabitants per day; Central America and the Caribbean: 408 S-DDD; South America: 735 S-DDD; Europe: 8,812 S-DDD; Oceania: 12,563 S-DDD; and North America: 30,814 S-DDD), and the equivalent of just 5 per cent of the licit per capita use of internationally controlled opioids at the global level.[181] The situation is further aggravated in West and Central Africa as most West African countries show licit per capita use of internationally controlled opioids even below the already extremely low African average of 174 S-DDD, including, in descending order, Cabo Verde, Ghana, Benin, Togo, Burkina Faso, Côte d'Ivoire, Chad, Nigeria and Sierra Leone. Data for the period 2015–2017 suggest that half of West African countries were using less than 4 S-DDD of internationally controlled opioids per million inhabitants over the period 2015–2017.[182]

Against this background of a de facto non-availability of internationally controlled opioids for pain medication for large sections of the population in West and Central Africa, tramadol – even though it is under national control in some West African countries – is in fact a widely available opioid in those countries, used for both medical purposes (including outside prescription) and for non-medical purposes.

Tramadol use is also reported in countries in Asia

The non-medical use of tramadol among other pharmaceutical drugs is reported by several countries in South Asia: Bhutan,[183] India,[184] Nepal[185] and Sri Lanka. In 2017, 130,316 capsules containing tramadol and marketed under the trade name "Spasmo Proxyvon Plus ('SP+')" were seized in Bhutan.[186] In Sri Lanka, about 0.2 per cent of the population aged 14 and older are estimated to have misused pharmaceutical drugs in the past year.[187] Among them, the non-medical use of tramadol is the most common, although misuse of morphine, diazepam, flunitrazepam and pregabalin have also been reported in the country. The misuse of more than one pharmaceutical drug (including tramadol) is also a common pattern among heroin users who may use them to potentiate the effects of heroin or compensate for its low level of availability.[188] Recent seizures of tramadol suggest the existence of a market for the drug: in April and September 2018, 200,000 and 1.5 million tablets of tramadol were respectively seized by customs in Sri Lanka.[189]

The 2019 drug use survey in India estimated that nearly 1 per cent of the population aged 10–75 had misused pharmaceutical opioids in the past year and that an estimated 0.2 per cent of the population (2.5 million people) were suffering from drug use disorders related to pharmaceutical opioids.[190] Although the breakdown by type of pharmaceutical opioids misused in India is not available, buprenorphine, morphine, pentazocine and tramadol are the most

180 Mohamed El Mahi, "Substance use problem in Sudan: elephant in the room", *British Journal of Psychiatry International*, vol. 15, No. 4 (November 2018), pp. 89–91.

181 *Estimated World Requirements for 2020: Statistics for 2018* (E/INCB/2019/2).

190 Atul Ambekar and others, *Magnitude of Substance Use in India 2019* (New Delhi, Ministry of Social Justice and Empowerment, 2019).

common opioids misused in the country.[191, 192]

In the Islamic Republic of Iran, a recent study estimated that about 7 persons per 1,000 population, or over 200,000 people aged 15–49 in urban centres had misused tramadol in the past year (2017), most of whom were young people.[193] An earlier study in 2012, which used a different methodology, estimated past-year prevalence at 11 per cent and past-month prevalence at 9.5 per cent for the non-medical use of tramadol among university students in one province in the country.[194] A systematic review of tramadol misuse and public health consequences in the Islamic Republic of Iran reported the past 12-month pooled prevalence of non-medical use of tramadol as 4.9 per cent among men and 0.5 per cent among women in the general population.[195, 196] The same study estimated the past 12-month pooled prevalence of non-medical use of tramadol among male university students at 4.8 per cent and 0.7 per cent among female students.

In recent years, cases of tramadol intoxication and fatal overdose, especially among young people who have a history of substance use disorder and psychiatric comorbidity, have been reported as a major cause of admission to emergency departments in Islamic Republic of Iran.[197, 198] Among these cases, tramadol had been misused with other substances, especially benzodiazepines. Some of the main conditions of tramadol intoxication that have been reported in the county include drug-induced seizures, depression of the central nervous and respiratory systems, and renal dysfunction.[199, 200] Another study that looked at tramadol overdose cases in the period 2013–2017 reported hypertension, tachycardia and seizures as the three main complications of tramadol intoxication and overdose.[201] The median age for tramadol overdose cases in the study was 41 years (range: 16–69) and the median tramadol dose resulting in intoxication was found to be 1,500 mg (range: 500–4,000 mg). The pooled prevalence of drug-induced seizures among tramadol-poisoning patients in the Islamic Republic of Iran was estimated at 35 per cent, ranging from 12.0 per cent to 69.3 per cent in different studies from 2005 to 2017.[202] Tramadol was also found to be the cause of death in around 6 per cent of the total drug overdose death cases in the Islamic Republic of Iran reported in different studies from 2006 to 2017.[203]

The non-medical use of tramadol is also reported by countries in East and South-East Asia, in some cases used in combination with other substances. In Indonesia, around 0.3 per cent of the adult population (10–59 years), or over half a million people, were estimated to have had past-year non-medical use of tramadol in 2017, while the past-year prevalence of non-medical use of tramadol among school students was 4.8 per cent.[204]

In Thailand, although population level data on the prevalence of non-medical use of tramadol is not available, the national treatment centre has reported an increasing number of people accessing treatment for opioid use disorders related to tramadol; they increased from 5 cases in 2014 to 46 cases in 2016 for tramadol only, and from 50 cases to 114 cases, over the same period, for those using a cocktail containing boiled kratom leaves, a cola-type soft drink, cough syrups containing codeine or diphenhydramine and tramadol or other anxiolytic drugs.[205] A retrospective study of patients aged 10–26 with drug-induced seizures who were admitted to emergency room departments in Bangkok from September 2011 to November 2013 found that the majority (90 per cent of the total of 56 cases) had used tramadol for non-medical purposes, with a

194 Saeed Bashirian, Majid Barati and Yadollah Fathi, "Prevalence and factors associated with tramadol abuse among college students in west of Iran: an application of the theory of planned behaviour", *Avicenna Journal of Neuropsycho Physiology,* vol. 1, No.1 (August 2014), pp. 26–30.

199 Samira Alinejad and others, "A narrative review of acute adult poisoning in Iran", *Iranian Journal of Medical Sciences*, vol. 42, No. 4 (July 2017), pp. 327–346.

200 Hossein Hassanian-Moghaddam and others, "Tramadol-induced apnea", *American Journal of Emergency Medicine*, vol. 31, No. 1 (January 2013), pp. 26–31.

201 Habibollahi and others, "Severe complications of tramadol overdose in Iran".

202 Rostam-Abadi and others, "Tramadol use and public health consequences in Iran: a systematic review and meta-analysis".

203 Ibid.

204 UNODC, responses to the annual report questionnaire submitted by Indonesia.

205 As reported in Tulaya Potaros and Suwimon Yeephu, "Recognition of tramadol abuse, dispensing practices, and opinions about its control policy among community pharmacists in Bangkok, Thailand", *Asian Biomedicine*, vol. 12, No.2 (April 2019), pp 91–99.

median dose of 400 mg. Most of the patients (80 per cent) examined were male with a median age of 17 years. While nearly half of the patients with drug-induced seizures had used tramadol only, the other half had misused it in combination with promethazine (25 per cent), hydroxyzine (16 per cent) and diphenhydramine (5 per cent).[206]

Is the non-medical use of tramadol and other pharmaceutical opioids emerging in Europe?

Recent data on treatment, drug-related deaths and seizures indicate that the non-medical use of tramadol is emerging in Europe. Although the current drug monitoring system at EMCDDA is limited in its capacity to detect and report on the availability, use and consequences of synthetic opioids, there are indications of an evolving threat of non-medical use of pharmaceutical and synthetic opioids in member States of the European Union.[207]

In the Netherlands, between 2008 and 2017 the rates of medical use of pharmaceutical opioids increased from 4,109 per 100,000 population in 2008 to 7,489 per 100,000 population. Of those, the number of tramadol users initially increased from 2,736 per 100,000 population in 2008 to 3,830 per 100,000 population in 2013 and declined to 3,494 users per 100,000 population in 2017.[208] Although not specified by substances, during the same period hospital admissions related to opioid intoxication also increased, as did the number of people in treatment of drug use disorders related to pharmaceutical opioids.[209]

A series of national surveys conducted in parallel in 2014 in Denmark, Germany, the United Kingdom, Spain and Sweden looked at the non-medical use of pharmaceutical drugs, including opioids.[210] Findings showed a past-year prevalence of non-medical use of pharmaceutical opioids ranging from 6.8 per cent in Spain to 2.9 per cent in Germany. The overall levels of non-medical use of pharmaceutical opioids in four countries, other than Germany, appeared to be at levels comparable to those in the United States.

Treatment demand related to opioids other than heroin is increasing

Data on treatment demand reported by EMCDDA show that in recent years the proportion of clients entering treatment for opioid use disorders other than heroin was 22 per cent of all primary opioid clients in treatment. Opioids other than heroin reported by treatment entrants included non-medical use of methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone.

206 R. Othong and W. Srisang, "Tramadol-induced seizures in adolescents and young adults in Bangkok: clinical features and emergency management", *Journal of the Medical Association of Thailand,* vol. 101, No. 8 (January 2018).

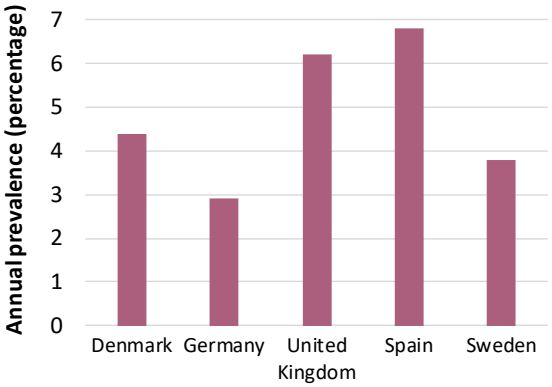
207 EMCDDA, *European Drug Report 2019*.

208 Gerard Arnoldus Kalkman and others, "Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study", *Lancet Public Health*, August 2019; 4: e498–505.

209 Arnoldus Kalkman and others, "Trends in use and misuse of opioids in the Netherlands".

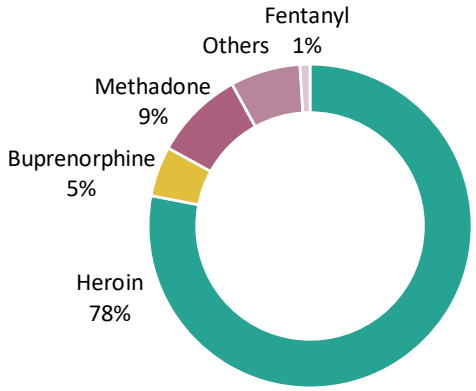
210 Scott P. Novak and others, "Nonmedical use of prescription drugs in the European Union", *BMC Psychiatry* (2016) 16: 274.

FIG. 49 Non-medical use of pharmaceutical opioids in the European Union, 2016



Source: Scott P. Novak and others, "Nonmedical use of prescription drugs in the European Union".

FIG. 50 Distribution of treatment demand for opioid use disorders in Western and Central Europe, 2018



Source: EMCCDA, *European Drug Report 2019*.

The non-medical use of pharmaceutical opioids, in particular tramadol, is also seen as an emerging problem among young people seeking treatment for opioid use disorder in Sweden. In a study among 73 treatment-seeking adolescents and young adults in an outpatient facility in Sweden, one third were found positive for tramadol misuse.[211] The adolescents also reported high rates of cannabis use and were also diagnosed with high rates of concurrent psychiatric problems.

Increasing threat of tramadol in Europe: overdose deaths attributed to tramadol on the increase in some countries

Overdose deaths attributed to tramadol are also reported by some countries in Western and Central Europe, including Latvia, Slovakia, Slovenia and the United Kingdom. In the European Union, at least 300 drug-related deaths were reported in 2017 in which tramadol was either present or implicated. In Latvia, in two thirds of the 27 deaths investigated by the State Centre for Forensic Medical Examination in 2017, the presence of opioids, primarily tramadol, morphine and methadone, was reported.[212] Similarly, in Slovakia, of the 19 drug overdose deaths reported in 2017, 15 were linked to opioids, primarily tramadol, and four to amphetamine or methamphetamine. The majority of overdose cases were among men aged 30 or older.[213] Slovenia, which reported a higher rate of drug related deaths (a rate of 3.2 deaths per 100,000 population) than the European average in 2017 (2.3 deaths per 100,000 population), also reported overdose deaths attributed to tramadol for the first-time.[214]

In Sweden, the overdose deaths attributed to opioids are quite diverse; in the distribution of opioid overdose deaths, after morphine there was a more or less equal share of other pharmaceutical opioids such as tramadol.

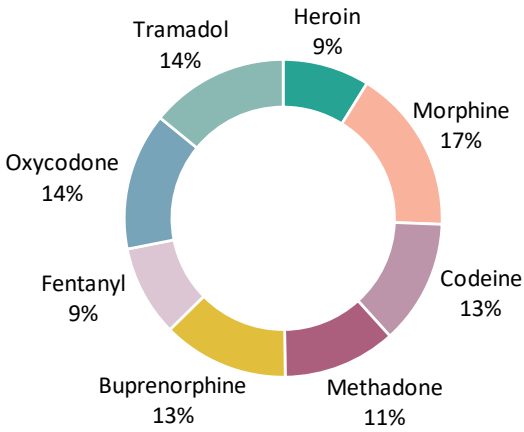
In Scotland, the total number of drug overdose deaths has increased considerably over the past 10 years, from 574 deaths in 2008 to 1,187 in 2018 (16 deaths per 100,000 population), when drug-related deaths increased by a quarter on the previous year. Out of those drug overdose deaths, nearly 80 per cent were attributed to opioids. Although small in number when compared with heroin overdose deaths, there was also a considerable increase in overdose deaths attributed to tramadol.[215]

The number of opioid overdose deaths has also doubled in Northern Ireland over the past decade, with the main increase seen in the absolute number of drug overdose deaths attributed to tramadol, which increased threefold from 2007 to 2017. However, the number of deaths attributed to fentanyls

214 EMCDDA, "Slovenia country drug report 2019" (Ljubljana, June 2019).

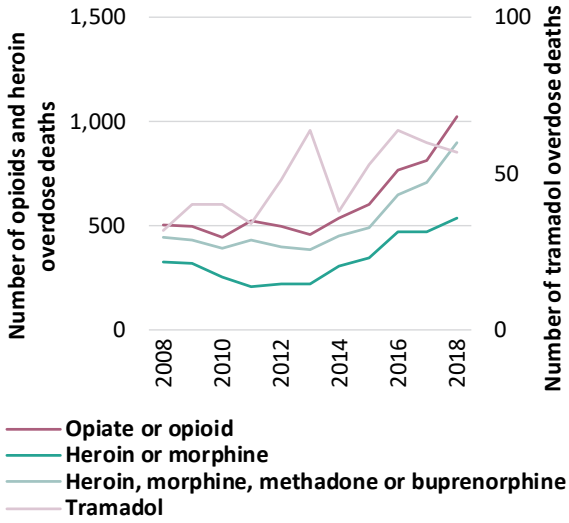
215 Tramadol was put under national control in Scotland in June 2014.

FIG. 51 Distribution of opioid overdose deaths in Sweden, 2016



Source: Håkan Leifman, Drug-related Deaths in Sweden: Estimations of Trends, Effects of Changes in Recording Practices and Studies of Drug Patterns, CAN Rapport No. 158 (Stockholm 2016).

FIG. 52 Trends in opioid overdose deaths in Scotland, 2008–2018



Source: United Kingdom, Office for National Statistics, Scotland.

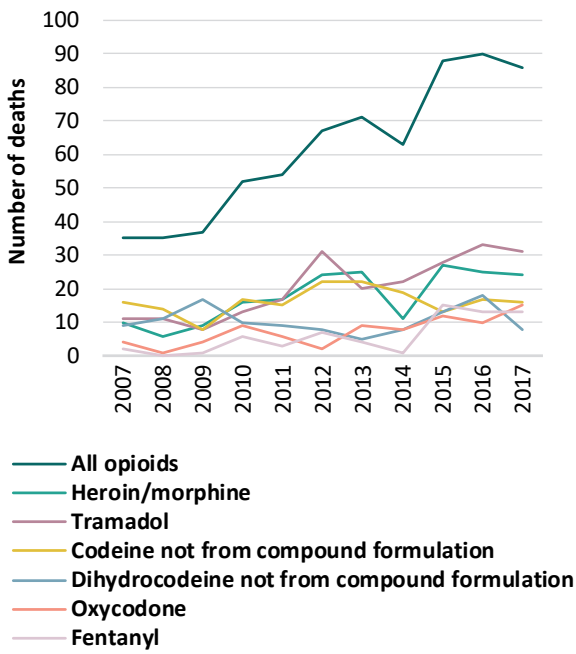
increased 6.5-fold and to oxycodone, 3.5-fold, over the same period.

Seizures of tramadol declined sharply in 2018 but remained concentrated in Africa and the Near and Middle East

Given that tramadol is widely used for medical purposes, it is challenging to define the magnitude of global trafficking of this substance because the non-medical market may be supplied through different channels: legitimate sales, diversion from legal trade and illicit manufacturing. Trafficking per se is also difficult to estimate due to its illicit nature. Data on seizures can give an indication of possible trafficking patterns, although they may be a result of changes in law enforcement priorities and/or capacities rather than changes in actual supply.

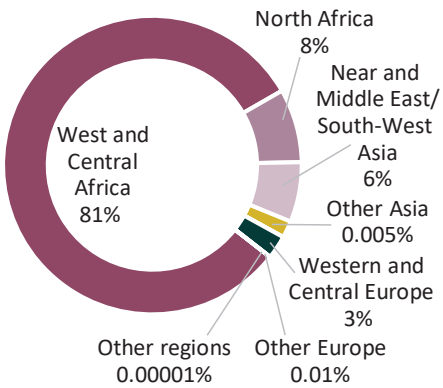
Rarely reported before, the quantities of tramadol seized have increased markedly since 2012, reaching a peak of over 125 tons intercepted globally in 2017 before declining drastically (-75 per cent) in 2018. The bulk of tramadol seized in the period 2014–2018 was seized in West and Central Africa (notably in Nigeria, Benin, Côte d'Ivoire and the Niger), followed by North Africa (notably Egypt, Morocco and the Sudan) and the Near and Middle East

FIG. 53 Opioid overdose deaths in Northern Ireland, 2007–2017



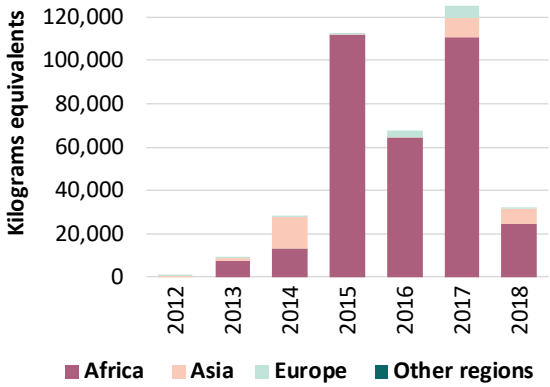
Source: Northern Ireland Statistics and Research Agency, "Drug-related and drug misuse deaths 2007–2017", 4 March 2019.

FIG. 54 Regional distribution of the quantity of tramadol seized, 2014–2018



Source: UNODC, responses to the annual report questionnaire.

FIG. 55 Global quantities of tramadol seized, 2012–2018



Source: UNODC, responses to the annual report questionnaire.

(notably Jordan and the United Arab Emirates). In some instances, countries in Western and Central Europe (notably Malta and Greece) have been used as transit countries for tramadol destined for North Africa (Egypt and Libya), although some of the tramadol seized in Europe (in particular Sweden) was also intended for the local market.

For the first time ever, significant seizures of tramadol were reported in South Asia (India) in 2018, accounting for 21 per cent of the global total that year, which reflects the fact tramadol was put under the control of the Narcotic Drugs and Psychotropic Substances Act of India in April 2018.[216, 217]

A decline in the quantities of tramadol seized at the global level, of 75 per cent compared with a year earlier, was seen in 2018, reflecting reductions in Africa, including in West and Central Africa (-77 per cent) and North Africa (-84 per cent) as well as in Asia, notably in the Near and Middle East/South West Asia (-99 per cent) and in Europe (-99 per cent). Although the reasons for a decline in drug seizures may be manifold, the fact that such marked declines happened uniformly across regions and subregions suggests that it was likely the result of a decrease in supply. As the full-scale scheduling of tramadol in India took place in 2018,[218] and India had been the main source for (illegal) tramadol shipments, the decline in seizures outside India in 2018 may have been the result of a disrupted market. By contrast, and probably as a result of the control in India, seizures of tramadol in that country increased greatly in 2018, and thus in South Asia as a whole (more than 1,000-fold compared with a year earlier).

Signs of a temporary shortage of tramadol in parallel drug markets in West and Central Africa in 2018–2019

A recent study on the trafficking of tramadol and other pharmaceutical opioids in West Africa has suggested a shortage of tramadol in the second half of 2018 and the first half of 2019, which was apparently linked to the scheduling of tramadol in India, and resulted in fewer shipments to West and Central Africa.[219] The new regulation in India in 2018 may have initially created a temporary increase in tramadol shipments to Africa, as companies cleared their stocks, followed by a sharp decline in the availability of tramadol on some illegal markets in West Africa, which went hand in hand with marked rises in the price of tramadol on those markets.[220] However, 59 tons of tramadol and 15.5 tons of falsified diclofenac

216 *Times of India*, ""ISIS drug" tramadol comes under narcotics law regulation", 29 April 2018.

217 UNODC, "At the crossroads of tramadol and other pharmaceutical opioids trafficking in West Africa" (July 2019), draft.

218 *World Drug Report 2019* (United Nations publication, Sales No. E.19.XI.8).

219 UNODC, "At the crossroads of tramadol", draft.

220 Ibid.

were seized in Benin from January to 31 May 2019,[221] which would suggest that large-scale tramadol trafficking continues in the region.

Another consequence of changes in the supply of tramadol has been the arrival of tablets in a parallel West African drug market, which were reportedly smuggled into the subregion from South Asia and sold there as "tramadol" but contained another painkiller, diclofenac. This substance, a non-steroidal anti-inflammatory drug, also known under the trade names Voltaren or Cataflam, is not an opioid and does not have any known psychoactive properties. Nonetheless, its misuse could have negative health consequences if too large a dose is taken. This could happen when recreational drug users expect psychoactive properties from their "tramadol" tablets and, when they do not obtain that effect, simply increase the dosage.[222]

221 Country report submitted by Benin to the Twenty-eighth Meeting of Heads of National Drug Law Enforcement Agencies, Africa (UNODC/HONLAF/28/CRP.11).

222 UNODC, "At the crossroads of tramadol", draft.