Contents

Rationale and methods 3
Multiple sources of supply 4
Divergent situations regarding use 5
Why more fentanyl use? 7
High levels of harm 7
Responding to fentanyl problems 9
Discussion 10
Conclusion 11
References 12

Acknowledgements


Report authors: Jane Mounteney, Michael Evans-Brown, Isabelle Giraudon.

EMCDDA contributors: Paul Griffiths, Laurent Laniel, Linda Maloney, Roumen Sedefov, Danica Thanki.
Rationale and methods

Concerns about the availability and use of the synthetic opioid fentanyl and its derivatives in Europe have been growing for some time. Reports of worryingly high levels of fentanyl use among injectors in Estonia have been increasing over the last decade (Ojanperä et al., 2008; Talu et al., 2010; Tuusov et al., 2012). In 2010 and 2011, in the wake of recent heroin shortages, Bulgaria and Slovakia identified opioid injectors using ‘China white heroin’ (widely assumed to be fentanyl). A recent increase in overdose deaths linked with use of fentanyl has been reported by Germany. In addition, in the 2011 Reitox national reports to the EMCDDA, a number of other EU Member States reported seizures of fentanyl as well as morbidity and mortality associated with the drug. Both concern at the high levels of mortality linked with fentanyl and uncertainty as to the extent of its use and availability warranted further exploration of the topic.

The EMCDDA Trendspotter case study on Fentanyl in Europe was undertaken during September and October 2012. It culminated in an expert meeting in Lisbon on 9–10 October 2012. The aim of the study was to increase understanding of the availability and illicit use of fentanyl in Europe, with a specific focus on: the extent and patterns of use; illicit production and diversion; harms and deaths; and, responses to the problem. Twelve experts from 10 EU Member States (Bulgaria, Czech Republic, Germany, Estonia, Greece, Italy, Slovakia, Sweden, Finland, United Kingdom) attended the meeting, presenting their experiences and contributing to an analysis of the topic, providing insights from law enforcement, forensics, treatment, research and monitoring, and drug user perspectives.

The Trendspotter study methodology incorporates a number of different investigative approaches and data collection from multiple sources. This study included: a review of the international literature; data collection from the 30 national early-warning systems (1); data

Background on fentanyl

Fentanyl is a narcotic analgesic with a potency at least 80 times that of morphine. Fentanyl and some of its derivatives (alfentanil, sufentanil, remifentanil and carfentanil) are used as analgesics and anaesthetics in human and veterinary medicine. They are subject to international control along with a few highly potent fentanyl derivatives that are not used medicinally, such as 3-methylfentanyl (TMF). On the European market both fentanyl and TMF are produced illicitly and are sold as either ‘fentanyl’, ‘China white’, ‘white heroin’ or simply ‘heroin’, with users sometimes unaware that it contains a fentanyl. In some circumstances, they may also be marketed as a replacement for heroin (such as ‘synthetic heroin’). Fentanyl-containing medicines are also diverted from the regulated supply chain.

A note on terminology

The focus of this report is the non-medical use of fentanyls that are sourced either as a result of illicit production or through the diversion of medicines. While it is recognised that the terms ‘misuse’ and ‘abuse’ are used for the purposes of the pharmacovigilance system, this report uses the term ‘use’.

For more information, see: www.emcdda.europa.eu/publications/drug-profiles/fentanyl

(1) http://www.emcdda.europa.eu/themes/new-drugs/early-warning
collection on fentanyl-related deaths cases; 12 expert presentations (from 10 countries); an electronic survey of experts attending the meeting; and, three facilitated working groups. Analysis was based on triangulation of the available data, with a view to providing as complete and verified a picture as possible. Bearing in mind important caveats — that much of the data are preliminary and many results are based on expert opinion and the grey literature — we present the following findings.

Multiple sources of supply

Fentanyl may be sourced from two principal routes: illicit production and diversion of medicines. Globally, there have been few reports to the United Nations Office on Drugs and Crime of seizures of illicit laboratories producing fentanyl over the past decade. Moreover, of those reported, information on the size and scale of production are rarely available. Data on the diversion of medicines containing fentanyl are also limited. The available data suggests that the illicit supply of fentanyl is intricately linked to the heroin market.

The emergence of the fentanyl on the illicit drug market in the European Union dates back to occasional reports from the mid-1990s. At that time, German authorities seized the precursors used to produce fentanyl, as well as o-, m-, and para-fluorofentanyl (Fritschi and Klein, 1995), while a large seizure of para-fluorofentanyl in the form of tablets, capsules and powders was made by authorities in the Netherlands (Poortman-van der Meer and Huizer, 1996). Around the same time, a seizure of capsules containing para-fluorofentanyl was also made in France (Poortman-van der Meer and Huizer, 1996). Since then no further reports of para-fluorofentanyl were identified in the literature.

A case report of a death in Italy in 1992 that details an overdose from fentanyl–cocaine use appears to be the first detection of fentanyl on the illicit market in the EU. However, it is unclear where the drug was sourced from (Ferrara et al., 1994). A case series of eight fatal overdoses that occurred between May 1994 and August 1995 in Sweden, at a time when fentanyl was being sold on the illicit drugs market as heroin or amphetamine (Kronstrand et al., 1997), provides further evidence of the early detection of the drug.

Aside from the seizure of para-fluorofentanyl in the mid-1990s, illicitly produced fentanyl detected on the European market have been limited to fentanyl and 3-methylfentanyl. It is not clear why other analogues that have been detected elsewhere, such as the United States (e.g. Henderson, 1988), have not been seen on the European market.

The first seizure of TMF in the European Union appears to have been in Finland in 2001. However, since then further detections in Finland have been isolated, with none in 2011 and 2012. Conversely, in Estonia, where the drug was first detected 2002, it has been detected on a more regular basis. For example, 1 kg of TMF along with 1.5 kg of fentanyl was seized in 2009. However, of note is a decline in detection of TMF in post-mortem biological samples (Tuusov et al. 2012). There have been few reports from other Member States of the detection of TMF.
More recently, in 2011, an illicit laboratory producing fentanyl was dismantled in Slovakia, with 4.4 kg of fentanyl seized (purity unknown). Those involved in the production and trafficking had links to organised crime, and were also involved in trafficking heroin and cocaine. Police intelligence notes that the fentanyl was trafficked to the Czech Republic, where 254 g (cut with paracetamol and caffeine) was seized in 2011. Subsequently, there have been no further seizures of fentanyl in Slovakia. In 2011, a large seizure (464 g) of fentanyl cut with quinine was made in Bulgaria while Greece seized a total of 700 g (purity unknown).

The diversion of fentanyl-containing medicines has also been reported in some EU Member States. Usually, it appears that these medicines are dosage forms that are more commonly available in outpatient settings, in particular transdermal patches. To a lesser degree, lozenges and sublingual tablets have also been noted. More occasionally, solutions of fentanyl intended for infusion have also been seized.

Divergent situations regarding use

Information on the illicit use of fentanyl in Europe is both patchy and scarce. As with findings on fentanyl availability, the evidence suggests diverse national situations with regard to the use of the drug. Many EU Member States have no data or reports (overdoses, deaths, treatment demands, seizures) to indicate that illicit use of fentanyl is occurring in any significant way. Some countries, primarily in the south and west of Europe, have reported one-off events, such as the dismantling of an illicit laboratory (Portugal in 2003), or what might be described as continuous ‘low level noise’ (Greece, Italy, United Kingdom), for example, in the form of occasional but relatively small numbers of fentanyl deaths cases or seizures. In the last two years, time-limited ‘outbreaks’ of fentanyl injection have been reported in Bulgaria (2010/2011) and Slovakia (Bratislava in 2011), linked with acute heroin shortages in both countries. Two northern European countries (Sweden, Finland) have reported localised increases in use of fentanyl and fentanyl-related deaths in recent years, indicating relatively high levels of use in certain populations of problem drug users. Germany (Bavaria) has documented worryingly high levels of fentanyl use among opioid users, evidenced by elevated numbers of fentanyl-related deaths. Estonia is a special case, and injecting use of fentanyls may be described as endemic in injecting drug user populations. Estonia has a documented history of fentanyl becoming the most commonly used opioid among injecting drug users over the last decade (Talu et al 2010, Vorobjov et al 2012).

The limited available data suggest that fentanyl use tends to be geographically localised and, for the most part, occurs in ‘pockets’, with its popularity and prevalence levels varying considerably from locality to locality. In Finland and Sweden, for example, the phenomenon is reported to be largely unknown in the capital cities; however, Turku (Finland) and Halland (Sweden) report higher numbers of users. Studies from Estonia show higher prevalence of use among injectors in Tallinn and the north-east of the country, while in Germany, Bavaria has considerably higher numbers of overdose cases reported than other regions.
Illicitly produced fentanyl derivatives are generally available as a powder which is dissolved and injected, smoked or inhaled. In addition, fentanyl derivatives in the form of small paper squares or ‘blotters’ (for ingestion), are reported to be available on the Internet. Fentanyl diverted from medical supply tends to be in the form of transdermal patches, but is also found in lozenges, buccal tablets and ampoules. Fentanyl transdermal patches can be misused in a variety of ways, with the drug extracted into a liquid and injected; placed in a glass container, heated and inhaled; smoked on foil; used on the skin; and cut into pieces and sucked or swallowed.

At the Trendspotter meeting, it was explained that in last 10 years, Estonian injectors have shifted from using homemade opiates and heroin, to illicitly produced fentanyls and amphetamine. Estonian overdose cases and seizures show that in different years, either fentanyl or TMF appeared to be predominant in the market. Most recent data supports the fact that both these substances are in circulation. In addition, while fentanyls continue to be the predominant opioids used by injecting drug users, there are also some reports of fentanyls being used by non-injectors in Estonia (Vorobjov et al 2012).

According to survey data, in 2008, the prevalence of ‘fentanyl’ use among the general population in Estonia aged 15 to 64 (last 12 months) was 0.1 % (1). Prevalence was higher (1.1 %) among young males (aged 15 to 24). Treatment demand data indicate that a high proportion of those entering treatment for drug problems in Estonia have fentanyl listed as their primary drug. 2011 data from the Estonian Drug Treatment Database identified 407 primary fentanyl/TMF users among all 532 registered clients (76.5 %). Fentanyl users also constituted 118 of the 163 clients entering treatment for the first time in their lives (72 %) in the same year (2).

With the exception of Estonia, very few EU Member States have data on levels and patterns of fentanyl use. The results of a small, and as yet unpublished, study of clients at three drop-in centres in Munich were presented to the Trendspotter meeting. Half of all survey participants (n=96) reported taking fentanyl, the majority injecting fentanyl which was sourced from transdermal patches. In addition, results from one published and two unpublished Finnish studies were presented at the meeting. One of these, focused on drug users in Helsinki (n=200), and identified only two marginalised respondents who had used fentanyl (Tammi et al., 2011). In a second (unpublished) survey, conducted at a needle exchange programme in Turku in 2011, 35 % of the sample (n=107) reported fentanyl use in the last year. Finally, in an unpublished 2012 survey of opioid substitution clients in Turku, 30 % of the sample (n=47) reported last year fentanyl use.

The few data available on the profile of fentanyl users suggests a mixed picture. Estonian fentanyl injectors have been identified as a marginalised, mainly ethnic Russian population, with multiple health and social needs. Toxicological reports show those dying of fentanyl-related overdose are mainly male and younger than other overdose cases. The Munich study of three low-threshold services noted that this sample of fentanyl users tended to be younger than non-fentanyl users. Surveys and toxicology reports show that, as with other

---

EMCDDA Standard Table No. 1, 2009.
(2) Drug Treatment Database, Estonian National Institute for Health Development.
Fentanyl in Europe

opioids, higher numbers of males than females appear to be users of fentanyl, and most are using several licit and illicit substances, in particular alcohol, benzodiazepines and other opioids. Outside of Estonia, fentanyl appears to be just one of a number of illicit substances consumed and is rarely the primary opioid of choice. In the Munich survey, less than 10% of respondents consumed only fentanyl, and none of those recruited in the Finnish studies exclusively used fentanyl.

Why more fentanyl use?

The Trendspotter meeting also explored the reasons for the increase in use of fentanyl in certain populations. The primary factors identified were the low availability, low purity or high price of heroin. In the Czech Republic, a temporary increase in the availability and use of fentanyl was linked to the establishment of an illegal laboratory in Slovakia. It was reported that for a period, low purity heroin was pushed out of the market by an influx of the more potent opioid. In countries reporting the use of fentanyls, opioid users described fentanyl as being more readily available, cheaper and stronger than heroin, but also more dangerous. And in this respect, fentanyl may also be a substance with its own ‘built-in brakes’ in some circumstances. German clients from the low-threshold agencies, for example, reported that fentanyl consumption is viewed as potentially life-threatening and the associated risks often considered too great. In addition, the fentanyl ‘high’ may fail to match the expectations of consumers when compared to other opioids (LaBarbera and Wolfe, 1983): with its effects being described by the German fentanyl users as ‘uninteresting’ and ‘boring’.

High levels of harm

Large numbers of fentanyl-related deaths have been reported in the United States (Centers for Disease Control and Prevention, 2008) as well as in Europe (particularly Estonia) in the past (Ojanperä et al., 2008). As part of this Trendspotter study, several countries reported case data on morbidity and deaths related to fentanyl use. Of these, Estonia, Germany and the United Kingdom reported the highest numbers of overdoses. There were approximately 650 reported deaths in the 2005–2011 period in Estonia, around 160 deaths reported in the 2007–2011 period in Germany, and around 50 deaths reported in 2001–2011 in the United Kingdom. Around 40 fentanyl-related deaths were reported in the 2008–2010 period in Finland, and, over this period, reports suggest a similar number in Sweden, although this still needs to be confirmed. Greece reported a low number of fentanyl-related deaths, with five since 2005.

Estonia stands out in terms of numbers of fentanyl overdose deaths and mortality rates due to the drug. Almost all cases are injectors and have used illicitly produced fentanyls. The victims are much younger (on average 28 years for women and 31 years for men)
compared to the overdose cases reported in Europe in general, where the average age is 38 years (EMCDDA 2011) (Figure 1).

In Germany, forensic and police sources documented increasing numbers of deaths related to fentanyl since 2007. In Bavaria, in particular, there are clear indications of an increase in fentanyl use among injecting drug users. The reported increases do not appear to be due to improvements in post-mortem screening for fentanyl.

In the United Kingdom, the picture is mixed and more complex. Where information is available, it appears that many of the deaths related to fentanyl may be linked with patients who were prescribed fentanyl patches to manage chronic pain. However, a number of cases show indications the drug has been extracted from patches and injected. The mean age of the United Kingdom victims is much older than in the Estonian cases (42 years overall in the United Kingdom, 47 years for women). Women accounted for 20 out of the 50 cases reported, which is higher than their usual share among drug overdose deaths in Europe (20%).

Toxicological data point to fentanyl use as being inextricably linked with polydrug use. Alcohol, illicit drugs and medicines (in particular, benzodiazepines) are frequently identified alongside fentanyl post mortem. Cases ascertainment, recording and coding of the cases are likely to differ between countries, and there is a probable underestimation of the presence of fentanyl in fatal overdoses, at least in some countries or regions.

In addition to the mortality data, there is evidence of morbidity associated with fentanyl use. In Estonia, users are at higher risk of HIV infection, sharing injecting equipment

**Figure 1:** Age and gender of fentanyl-related overdose deaths in Estonia, 2011 (n=105)
and experiencing serious overdoses compared to those who inject other drugs (Talu et al., 2010). Furthermore, morbidity associated with the use of fentanyl in the context of polydrug use might be in part unrecognised. For example, in Italy, around 10 non-fatal fentanyl overdoses were reported since 2006 through emergency departments at hospital and poison centres, but fentanyl is not systematically searched for in these settings, and thus, its implication in non-fatal overdoses might be underestimated.

### Responding to fentanyl problems

At country level, the most appropriate responses to the illicit supply and use of fentanyl will depend on the nature of the problem. The options discussed at the Trendspotter meeting ranged from providing warnings and information to users and practitioners, law enforcement action, regulating prescriptions, environmental health interventions, as well as drug treatment provision and harm reduction initiatives. One example discussed at the meeting was the coordinated response to a fentanyl outbreak in Bratislava, where law enforcement agencies in Slovakia dismantled an illicit production laboratory, and health services simultaneously targeted information and advice to users.

In the case of Estonia, the importance of improving the general health and social conditions for fentanyl injectors was identified as a priority area for intervention. In addition, increasing access to opioid substitution treatment for those with fentanyl dependence was seen as a key priority. In terms of reducing overdose deaths, there was a call for raising the profile of the problem, ensuring that naloxone is available to users and families, as well as a request for EU-level guidelines on overdose prevention.

In terms of law enforcement responses, a better understanding of illicit fentanyl production sites and supply routes is required. In some cases, the dismantling of illicit production laboratories appears to have been effective in ending outbreaks of fentanyl use. This has also been the case in US outbreaks (Centers for Disease Control and Prevention, 2008). However, if production occurs in neighbouring countries outside of the European Union, for example in Russia, Belarus or the Ukraine, seizures are likely to be more limited and laboratories may lie outside Member States’ jurisdiction. This will require increased cooperation with third countries, border controls and customs authorities. In addition, the value of enhanced forensic investigation was highlighted, including the capability and capacity to identify fentanyls (over 1 000 possible), improved data on the purity of seized and collected samples, as well as the need for impurity profiling (to improve insights into synthetic routes including the precursors used).

The diversion of fentanyl-containing medicines takes a number of forms and requires a range of responses. Reports suggest that transdermal patches, in particular, may be diverted in a number of ways, including: theft from pharmacies; collection from the waste of the hospitals and elderly units; unused patches not returned and being sold by relatives; patients selling patches; both misuse and sale by medical staff such as anaesthetists and nurses; inappropriate or over-prescribing by clinicians; and, patients using multiple and fraudulent prescriptions (such as from ‘doctor shopping’).
Findings suggest that responses should strengthen vulnerable points in the system, associated with prescribing, patient behaviours, and disposal of medical waste. With regard to diversion and misuse by medical staff, vigilance in healthcare settings is important. In addition, close monitoring of prescriptions by health authorities is indicated in areas where over-prescribing or ‘doctor shopping’ is a concern. A need for clear prescribing guidelines was one important conclusion of a working group responding to the Bavarian outbreak. The adequate disposal of medical waste is one area that is reasonably straightforward for health authorities to address. Systems need to be in place to ensure that each time a fentanyl patch is removed from a patient, it is disposed of in a safe and secure manner. Similarly, ‘take back’ schemes for unused medicines from patients should be in place in order to limit diversion.

Discussion

In the European Union, Estonia has the longest documented epidemic of fentanyl injection among drug-using populations. This has been accompanied by high levels of overdose deaths and increased risk of HIV infection among users. Apart from a growing body of evidence on the Estonian situation, European data on fentanyl availability and use remains partial and inadequate. The Trendspotter exercise highlighted problems linked to missing fentanyl-related data and the need to improve a number of information sources, including:

- increasing understanding of fentanyl overdoses and how to reduce these (in combination with other substances);
- improving early detection and early warning capacity — with regard to market changes, new production, Internet sales etc.;
- developing forensic impurity profiling; and,
- more qualitative research to improve understanding of user motivations, etc.

A specific data-related problem raised is the fact that poisonings due to fentanyl do not have a specific ICD 10 code. One of the countries participating in the meeting reported that a request had been made to the World Health Organization for improvements here.

What is clear from this study is that even at very low prevalence, the public health impact of fentanyl may be considerable. The analysis suggests that in the overall EU context, fentanyl can be described as a ‘low use but high risk/harm’ substance. Estonia stands out from other countries, having a longer and more deeply engrained history of fentanyl injection among problem opioid users, and associated high levels of fentanyl-related deaths.

Rapid increases in fentanyl use may be more likely to occur among problem opioid user populations at the sub-national or regional level, as documented here in Bavaria, Halland and Turku. In this context, we note that there are some indications in Europe that the conditions conducive to future fentanyl outbreaks are probably growing. Evidence suggests that Europe is increasingly being seen as a less attractive market for heroin, and
may well be in the grip of a gradual, and possibly long term decline in heroin availability (EMCDDA, 2012). Our experience over the last decade shows that heroin shortages can leave the way open for synthetic opioids (fentanyl, buprenorphine, methadone) to fill the market gap as replacement products.

With regard to diversion of medicines, policy responses need to take into account the important legitimate use of fentanyl as an analgesic. Some European countries are struggling to provide adequate access to appropriate levels of analgesics for patients (World Health Organization, 2011). It is important in this context that any consideration of further regulation of opioids such as fentanyl does not hinder progress towards universal provision of appropriate medical pain management. In addition, Europe’s economic problems are likely to result in increased palliative care taking place in domestic, rather than hospital, settings. As a result, the challenges for controlling access to pain medicines are likely to increase. It is worth noting the findings of a recent Finnish study, which found that the use of fentanyl patches among lonely elderly people is an increasing problem (Bell et al., 2009).

There remains a need to extend this review of fentanyls to other EU countries. In addition, the analysis has highlighted questions for future discussion: is the appearance of fentanyl on the illicit market in some Member States a one-off appearance or the start of a trend? What constitutes optimal treatment for fentanyl users?

Conclusion

A key conclusion from the study has been the recognition that fentanyl use outbreaks may be both symptomatic of, and probably just the tip of the iceberg in, Europe’s growing synthetic opioid use problem. In many respects, the fentanyls case study can be seen as a microcosm of Europe’s complex contemporary drug market, incorporating three key dimensions: illicit production and use, the diversion and misuse of medicines, and the Internet sale of non-controlled new psychoactive substances. Fentanyl use has a clear illicit component, with production of ‘China white’ reportedly occurring both in countries bordering the European Union and occasionally within Member States themselves. A second major angle identified in this study has been the diversion and misuse of fentanyl-containing medicines — particularly transdermal patches — in many of the regional outbreaks. Finally, this study has identified that fentanyl and its analogues can be linked with chemical innovation, rapid diffusion and a fluid global drug market. Most fentanyls remain little understood, potentially lethal, and their availability on the Internet may be on the increase.
References


