



Commentary

Fentanyl: Are we missing the signs? Highly potent and on the rise in Europe

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ABSTRACT

Fentanyl is a synthetic opioid analgesic historically used as a pain reliever and an anaesthetic. Recent concerns have arisen around the illicit use of fentanyl and its analogues in a number of European countries, linked to their high potency and associated risk of fatal overdose. Evidence has been emerging from Estonia for over a decade of entrenched patterns of fentanyl use, including injection of the drug and hundreds of overdose deaths. More recently, reports indicate that both fentanyl and 3-methylfentanyl (TMF) have been marketed as a replacement for heroin in European countries (e.g. Bulgaria, Slovakia) affected by heroin shortages. In addition, Germany, Finland and the United Kingdom, reported new outbreaks of fentanyl-related deaths. This combination of increasing mortality data alongside law enforcement intelligence suggesting both diversion and illicit production of fentanyls, prompted wider investigation using a targeted multi-source data collection exercise and analysis. This identified that in the European context, fentanyls are 'low use but high risk/harm' substances. Evidence shows that Estonia stands out as having an endemic problem, while the use of fentanyls in other European countries appears to be geographically localised. Developments in illicit supply of fentanyls reflect the complexity of Europe's contemporary drug market: manifesting illicit production and use, the diversion and misuse of medicines, and the online sale of non-controlled new psychoactive substances. Likewise effective and integrated responses will need to address fentanyl production, diversion as well as ensuring the availability of harm reduction measures to users.

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Key points

Fentanyl is a synthetic opioid analgesic historically used as a pain reliever and an anaesthetic.

Recent concerns have arisen around the illicit use of fentanyl and its analogues in Europe, linked to their high potency and associated risk of fatal overdose.

The illicit supply of fentanyls onto Europe's drug market includes illicit production, the diversion of medicines, and the online sale of non-controlled new psychoactive substances.

In Europe, Estonia stands out as having an endemic problem, with entrenched patterns of fentanyl use, including injection and associated high mortality rates.

The use of fentanyls in other European countries appears to be geographically localised. However, both fentanyl and 3-methylfentanyl (TMF) have been marketed as a replacement for heroin

in countries affected by recent heroin shortages (e.g. in Bulgaria, Slovakia).

In addition Germany, Finland and the United Kingdom, have also reported recent outbreaks of fentanyl-related deaths.

Overall in the European context, this study finds fentanyls to be 'low use but high risk/harm' substances.

Integrated responses are required to ensure the availability of harm reduction to users as well as address fentanyl production, and diversion.

Fentanyl in Europe

Fentanyl is a synthetic opioid analgesic acting predominately at the μ -opiate receptor. It has historically been used as a pain reliever and an anaesthetic in both human and veterinary medicine and in terms of analgesic activity it is at least 80 times more potent than morphine. Fentanyl was first synthesized by Paul Janssen in 1960 and marketed as a medicinal product for treating pain. Subsequently, many fentanyl analogues were developed including

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sufentanil, alfentanil, remifentanil, and carfentanil. Fentanyl was first introduced for widespread palliative use in the mid-1990s in the form of transdermal patches, and to this day, it continues to be an important and much prescribed pain management medication in many countries. Concern surrounding the fentanyls is linked to their potential for dependence and misuse, their high potency and associated risk of fatal overdose. A small but growing literature documents problems internationally with these substances, notably in the United States (Centers for Disease Control and Prevention, 2013; Mercado-Crespo, Sumner, Spelke, Sugerman, & Stanley, 2014) Australia (Roxburgh et al., 2013) and Canada (Fischer, Jones, Urbanoski, Skinner, & Rehn, 2014).

The first documented large scale fentanyl outbreak was in the United States mainly in California between 1979 and 1988, with 112 deaths linked to the use of alpha-methylfentanyl. The first evidence of problems in Europe came with reports of eight fentanyl-related deaths identified in Sweden in 1994 (Kronstrand, Druid, Holmgren, & Rajs, 1997), however evidence has been emerging from Estonia over the last decade of entrenched patterns of fentanyl use, including injection of the drug and reports of hundreds of overdose deaths (EMCDDA, 2014; Ojanperä, Gergov, Liiv, Riikoja, & Vuori, 2008; Talu et al., 2010; Tuusov et al., 2012; Uuskula, Rajaleid, Talu, Abel-Ollo, & Des Jarlais, 2013). More recently, reports indicate that both fentanyl and 3-methylfentanyl (TMF) were being marketed as a replacement for heroin and sold as either 'fentanyl', 'China white', 'white heroin' or simply 'heroin' in several European countries (Bulgaria, Slovakia) affected by heroin shortages (Griffiths, Mounteney, & Laniel, 2012). During the same period, Germany, Finland and the United Kingdom, all countries with no previously documented history of misuse of the drug, reported outbreaks of fentanyl-related deaths.

Concerns regarding increasing mortality associated with consumption of fentanyls, alongside law enforcement intelligence suggesting both diversion and illicit production of the drugs, prompted wider investigation of the phenomenon by the EMCDDA, in order to understand the magnitude of the problem and to inform policy responses. To this end, a scoping study involving a targeted multi-source data collection exercise on the fentanyls was undertaken during the summer of 2012, culminating in a 'synthesis' meeting in Lisbon in October. This included: a survey among national early-warning systems in 30 countries¹; collection of fentanyl-related deaths cases data from seven countries where problems had been identified (Estonia, Finland, Germany, Greece, Italy, Sweden, the United Kingdom); and a review of the international literature on fentanyls. In addition national experts from law enforcement, forensics, treatment provision, qualitative research and drug user representatives provided contextual information, via an electronic survey, semi-structured presentations and facilitated focus groups. This approach is designed to critically explore the available information on emerging threats or developments. It is taken that the information will be partial and incomplete. Whilst proving timely and valuable insights, the approach has obvious weaknesses, based on the incompleteness on the information available. Therefore, interesting hypotheses can be generated for follow up research and a useful purpose is served by auditing the information available on the situation, but caution must be exercised in over-inferring from the data available. More details of the methodology can be found elsewhere (EMCDDA, 2012). Results presented in this paper are based on analysis and triangulation of the statistical and qualitative data sources, with new data incorporated where this has become available.

Fentanyls supply to illicit markets in Europe, both illicit production and diversion of medicines

In Europe, fentanyl and its derivatives (fentanyls hereafter) destined for the illicit market appear to be sourced from two principal routes: via illicit production and from diversion of fentanyl-containing medicines from the regulated supply chain. Currently available data indicate it is primarily fentanyl and 3-methylfentanyl (TMF) that are being illicitly produced often in countries bordering the EU (Russia, Belarus and the Ukraine), and transported to neighbouring European countries, in particular Estonia. Within the EU, illicit production is less common, however production facilities have been seized in Bulgaria, Greece and Portugal. In addition, an illicit laboratory producing fentanyl was dismantled in Slovakia in 2011, with 4.4 kg of powder fentanyl seized (purity unknown). To provide some context as to the potency of the drugs, it is estimated that 2.5 g of pure 3-methylfentanyl is enough to produce 10,000 doses (EMCDDA, 2014).

Alongside illicit production, the other main source of fentanyls that are misused in Europe is the diversion of fentanyl-containing medicines. Most commonly this involves fentanyl transdermal patches, and, to a lesser extent, lozenges, sublingual tablets, and solutions of fentanyl intended for infusion. This diversion encompasses a number of practices including: inappropriate or over-prescribing by clinicians; theft from pharmacies; collection from the waste of hospitals and geriatric units; unused patches being sold by patients and relatives; both misuse and sale by medical staff such as anaesthetists and nurses; and, patients using multiple and fraudulent prescriptions. 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; or cut into pieces and sucked or swallowed. Commentators have documented elsewhere the extent to which the misuse of medicines in Europe, where opioid prescribing by pain clinics is not a feature, differs from the patterns and trends identified in US analyses (Griffiths, Evans Brown, & Sedefov, 2014).

Divergent situations regarding patterns and prevalence of use

Any discussion of the illicit use of fentanyl needs to be prefaced by the recognition that this drug plays an important role in pain medicine in many countries. The International Narcotics Control Board (INCB) collect and report international data on the legitimate distribution of fentanyl for medical and scientific purposes, presented as fentanyl consumption data per capita. This provides an interesting European backdrop to investigation and understanding of patterns of illicit use. It is important to note that consumption as used here refers to amounts distributed to the retail level, not the amounts dispensed to, or used by, patients. As is evident in Fig. 1, distribution varies widely between countries with Germany topping the INCB euro consumption table for 2011, while Estonia has one of the lowest rates among EU countries. This information is consistent with both forensic and law enforcement reports that most fentanyl misuse in Germany is linked with diverted pharmaceuticals, in particular transdermal patches, while most fentanyl misuse in Estonia involves illicitly produced fentanyls.

Of all European countries, Estonia has the most entrenched and best documented situation regarding illicit fentanyls use. In the early 2000s a number of European countries reportedly experienced severe disruption to heroin availability – purportedly at least partially linked to imposition of Taliban controls on opium production – leaving irrevocable market changes. This period saw the rise of fentanyl use in Estonia, buprenorphine use in Finland, and probably affected other countries too (Griffiths et al., 2012). Over the last decade, fentanyls have become Estonia's most

¹ <http://www.emcdda.europa.eu/activities/actions-on-new-drugs>.

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