Neuroscience and Biobehavioral Reviews 106 (2019) 133–140

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

New synthetic opioids: Part of a new addiction landscape

Laurent Karila[a,*], Maude Marillier[b], Boris Chaumette[c], Joel Billieux[g], Nicolas Franchitto[d,e], Amine Benyamina[f]

[a] Addiction Research and Treatment Center, Paul Brousse Hospital, Paris-Sud University, INSERM U1000, Villejuif, France
[b] Addictogilance center (CEIP-A), Fernand Widal Hospital, Paris, France
[c] Montreal Neurological Institute and Hospital, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada
[d] Addiction center, Centre Hospitalo-Universitaire Toulouse-Purpan, Toulouse, France
[e] UMR1027, Université de Toulouse, UPS, INSERM, Toulouse, France
[f] Addiction Research and Treatment Center, Paul Brousse Hospital, Paris-Sud University, CESP, Villejuif, France
[g] Addictive and Compulsive Behaviours Lab, Institute for Health and Behaviour, University of Luxembourg, Esch-sur-Alzette, Luxembourg

ARTICLE INFO

Keywords:
Fentanyl
Synthetic opioids
New psychoactive substances
AH-7921
MT-45
U-47700
Adverse effects
Psychiatric complications
Somatic complications
Substance use disorder
Fatalities

ABSTRACT

Synthetic opioids (SO) are a major risk for public health across the world. These drugs can be divided into 2 categories, pharmaceutical and non-pharmaceutical fentanyls. A new generation of SO has emerged on the drug market since 2010. North America is currently facing an opioid epidemic of morbi-mortality, caused by over-prescription of opioids, illegally diverted prescribed medicines, the increasing use of heroin and the emergence of SO. Furthermore, this opioid crisis is also seen in Europe. SO are new psychoactive substances characterized by different feature such as easy availability on the Internet, low price, purity, legality, and lack of detection in laboratory tests. They have not been approved or are not recommended for human use. Opioid misuse is associated with somatic and psychiatric complications. For many substances, limited pharmacological information is available, increasing the risk of harmful adverse events. Health actors and the general population need to be clearly informed of the potential risks and consequences of the diffusion and use of SO.

1. Introduction

Synthetic opioids (SO) are a major risk for public health and a real challenge for drug policies across the world. They can be divided into 2 categories, pharmaceutical fentanyls (such as fentanyl, sufentanyl, remifentanyl, and alfentanyl) and non-pharmaceutical fentanyls (NPF) which are fentanyl analogues or designer fentanyls (such as ocfentanyl, butyrfentanyl…). A new generation of SOs, structurally different from fentanyl, has emerged on the drug market since 2010. Among them are AH-7921 (benzamide analogue), MT-45 (piperazine analogue), or U-47,700 (isomer of AH-7921).

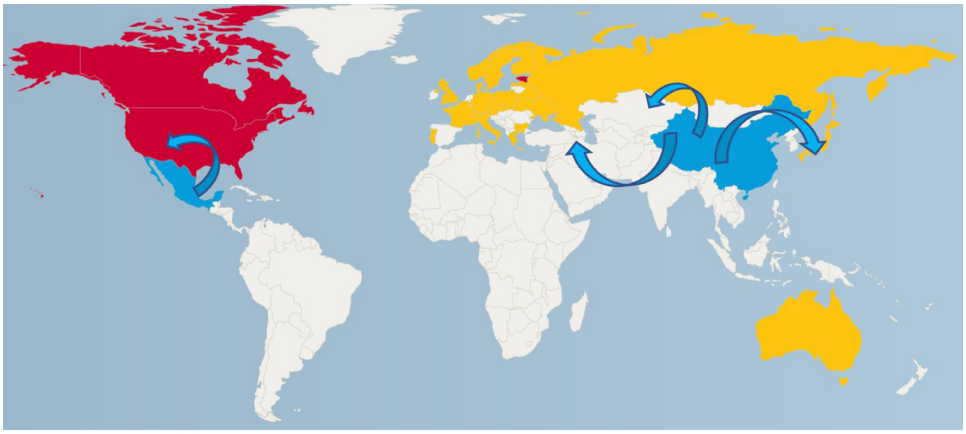
North America is currently facing an opioid epidemic of morbi-mortality. This crisis, caused by over-prescription of opioids, illegally diverted prescribed medicines and the increasing use of heroin, is also linked to the emergence of SOs, most of which are derived from fentanyl. In 2015, the US Drug Enforcement Administration (DEA) published a nationwide warning about the dangers of fentanyl and fentanyl-related compounds, completed by an official health advisory document released by the Centers for Disease Control (DEA, 2015) (NDEWS, 2015). However, this opioid crisis is not an isolated phenomenon and as a public health problem is becoming increasingly harmful in Europe (Figs. 1–3).

Fentanyl and SOs are often illegally imported from countries such as China or Mexico. New SOs were initially developed for therapeutic purposes, but are now produced in uncontrolled clandestine laboratories. From inexpensive and readily available precursors such as 4-anilino-*N*-phenethylpiperidine (ANPP) and *N*-phenethyl-4-piperidone (NPP), some SOs such as acetylfentanyl, butyrfentanyl and furanylfentanyl can be produced using a fairly simple synthesis method. In March 2017, ANPP and NPP were scheduled under international control (UNODC, 2017). Some laboratories have already been dismantled in the USA, Canada, Russia, and Europe (Germany, Slovakia, Portugal) (UNODC, 2017). Adulterated heroin purchased on the darknet has been found to be in fact ocfentanyl (Quintana et al., 2017). SOs can be sold on the Clearnet but black markets on the darknet also exist.

SOs are new psychoactive substances (NPS) with features such as easy availability on the Internet, low price, purity, legality (for some of them), or lack of detection in laboratory tests. Between 2009 and 2016, 25 new SOs were detected on the European drug market. These include

* Corresponding author at: Addiction Research and Treatment Center, Paul Brousse Hospital, 12 avenue Paul Vaillant Couturier, Villejuif, France.
E-mail address: laurent.karila@aphp.fr (L. Karila).

https://doi.org/10.1016/j.neubiorev.2018.06.010
Received 16 February 2018; Received in revised form 14 May 2018; Accepted 12 June 2018
Available online 12 September 2018
0149-7634/



- Countries in blue: Main manufacturers
- Countries in red: Opioid crisis
- Countries in yellow: Public health issue
- Not colored: No data available

Fig. 1. Opioid use situation around the world.
Countries in blue: Main manufacturers.
Countries in red: Opioid crisis.
Countries in yellow: Public health issue.
Not colored: No data available.

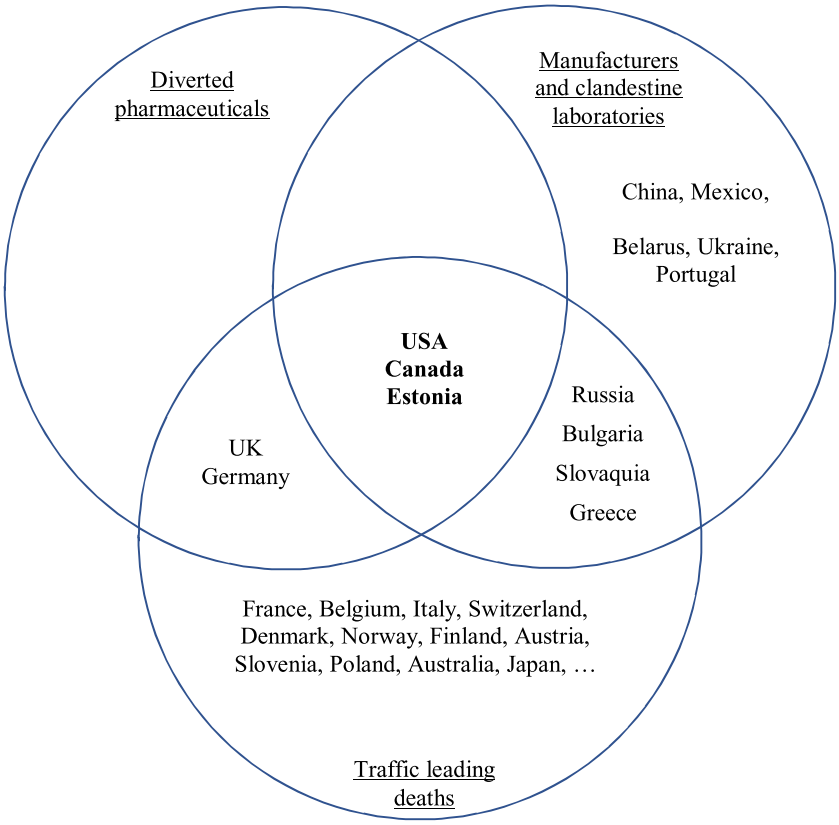


Fig. 2. Non-exhaustive Venn Diagram of epidemiological data of synthetic opioids.

18 fentanyl analogues, eight of which were detected for the first time in the last year (EMCDDA, 2017a). In 2016, SOs amounted to 4% of NPS while the proportion was f 2% in 2014.

SOs are found in powder, tablet or liquid forms. As for the majority of NPS, users can swallow, snort, smoke or inject them. They can also use blotter papers (NIDA/NIH, 2016). Acetylfentanyl in the form of a nasal spray and MT-45 powder in herbal smoking mixtures associating synthetic cannabinoids have already been found (EMCDDA, 2017a). Rectal or sublingual routes of administration have also been reported, as for example with AH-7921 (Coppola and Mondola, 2015). SOs can also be vaped with an electronic cigarette (Rogers, Rehrer et al. 2016), smoked using burning powder or aluminium foil (chasing the dragon), and inhaled using a vaporizer (Prekupec, Mansky et al. 2017).

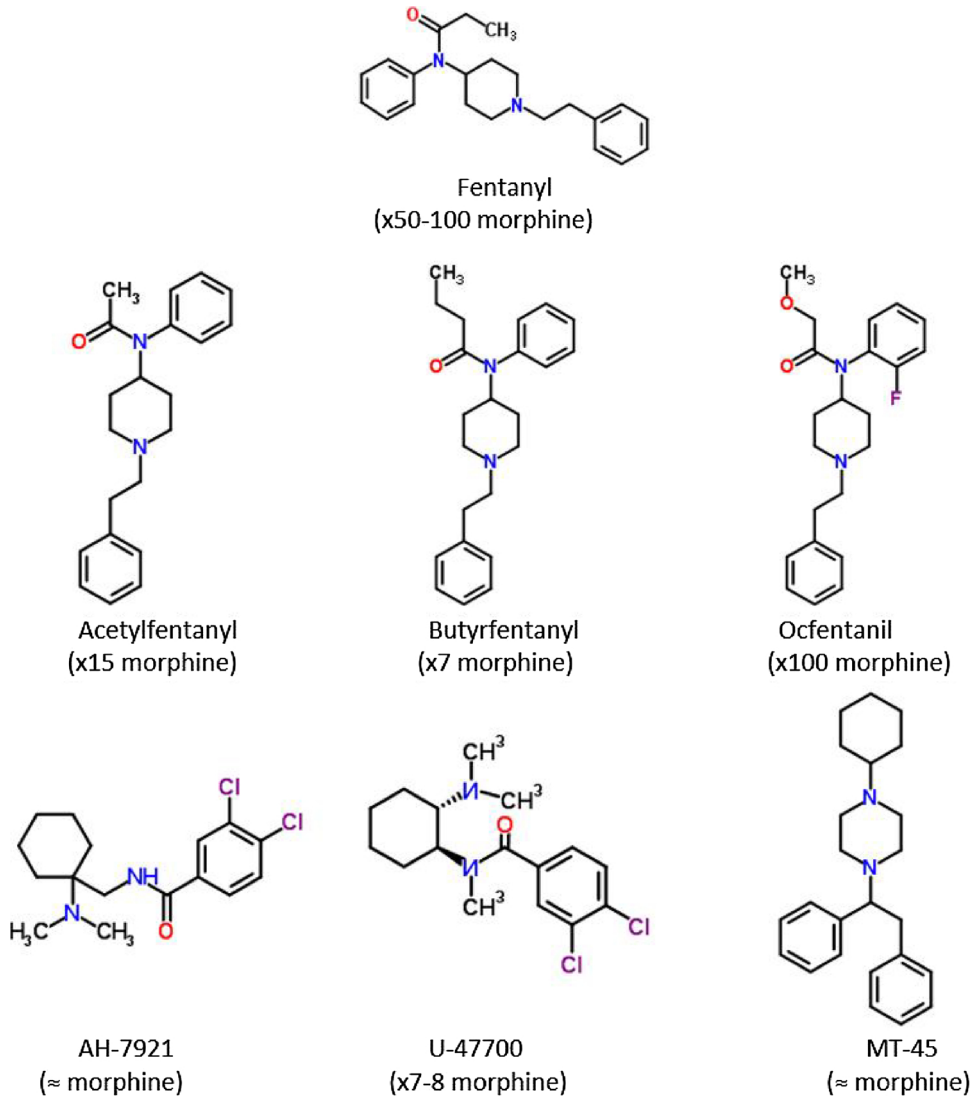


Fig. 3. Structural differences and potency of parent Fentanyl and some SOs.

Many of the SOs have not been approved or are not recommended for human use (Zawilska, 2017). Illicit opioid use is associated with dangerous somatic and psychiatric complications, either on account of their actual nature, or because of adjuvants or impurities. The content of illicit opioids is not always known and many users are not aware of what products they are using. For many of these substances, there is limited pharmacological information available, increasing the risk of harmful adverse events (Madras, 2017).

Health actors and the general population need to be clearly informed of the potential risks and consequences of the diffusion and use of SOs. In this paper, we set out to review the available data on the use and effects of SOs in humans in order to highlight their impact on public health. A literature search was based on PubMed, Google Scholar, Erowid, government websites, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA, Lisbon), Early Warning Reports from European Union (EU-EWS), National Reitox, and the United Nations Office on Drugs and Crime (UNODC), using the following keywords alone or in combination: “fentanyl”, “synthetic opioids“, “new psychoactive substances”, “AH-7921″, “MT-45″, “U-47700″, “adverse effects”, “psychiatric complications”, “somatic complications”, “substance use disorder”, “fatalities”. The literature search led to the identification of 69 potentially relevant articles. All articles were screened from their abstracts to determine their relevance in the framework of the current review.

2. Epidemiological data

SOs are mainly sold as heroin, adulterated heroin or counterfeit medicines (fake drugs such as oxycodone). They can be used as medicines, counterfeit medicines, traditional illicit drugs or research chemicals (RC). SOs have also been reported to be sold as substitutes for heroin in case of shortages, for instance in Bulgaria and Slovakia (NDEWS, 2015). Counterfeit medicines are not subjected to any pharmaceutical quality control. One kilogram of new SO enables the production of hundreds of thousands of counterfeit tablets. From 2014 to 2015, 7000 pills sold as oxycodone were characterized as fentanyl or a combination of heroin and fentanyl. In 2016, 6000 other pills were identified as fentanyl citrate or acetyl fentanyl, and 500 others as U-47,700 (DEA, 2016). Counterfeit alprazolam pills, containing fentanyl and in some cases etizolam were also reported and some deaths have occurred, among which 9 cases in Florida in the first three months of 2016 (Arens et al., 2016). In March and April 2016, tablets sold as hydrocodone and acetaminophen (Norco) induced 52 non-fatal intoxications and 10 deaths reported in the United States. Pills were also reported to contain fentanyl, ranging from 0.6 to 6.9 mg per pill, while the lethal dose for a non-opioid user is considered to be 2 mg (DEA, 2016) (Sutter et al., 2017).

SOs can also be sold as illicit drugs or RC. Most often, they are sold mixed with heroin or as heroin. Under the name “china white”, “tango

& cash", "synthetic heroin", RCs appeared in the 1970 s in North America (Henderson, 1991). Samples of cocaine and ecstasy have already been shown to contain fentanyl (Lucyk and Nelson, 2017). In British Columbia, an epidemic of 43 intoxications from crack/cocaine adulterated with furanylfentanyl were reported over a 4-day period in June 2016 (Klar et al., 2016). Regarding RCs, "Synthetic opium" bought on the Internet revealed the presence of acetylfentanyl (Rogers et al., 2016).

SOs can also be diverted from pharmaceutical medicines. Fentanyl is used in human therapy for the management of severe pain and in anaesthesia. Sufentanyl, remifentanyl, and alfentanyl are also used in anaesthesia. Carfentanyl, which is at the moment the most powerful synthetic opioid (10 000 times more potent that fentanyl) is used in veterinary medicine. Pharmaceutical forms include transdermal patch, lozenges, sublingual tablets, and solutions for infusion. Fentanyl can be extracted from patches for injection, ingestion and inhalation (EMCDDA, 2012).

The first cases of serious abuse of fentanyl were recorded in the USA, between 1979 and 1988 with the emergence of alpha-methylfentanyl sold on the street drug market as "china white" or "synthetic heroin" (Zawilska, 2017). The number of exposures reported to the American Association of Poison Control Centers dramatically increased from 300 cases in 2010 to more than 1400 in 2014 (Zawilska, 2017). Since August 2016, carfentanyl alone has caused more than 300 intoxications, probably in a context of adulterated heroin powder use. In Canada, the first alert about the potential harm of fentanyl was issued in 2013 by the Canadian Centre on Substance Abuse. In 2014, the same center alerted to the existence of counterfeit tablets of oxycodone containing fentanyl.

According to a retrospective study of overdose in a Medically Supervised Injecting Center (MSIC) in Sydney, the number of fentanyl injections increased by 1000% between 2012 and 2015. Of an average of 40 opioid overdoses usually reported per month, 7 were caused by fentanyl from late 2014 (Latimer et al., 2016).

In Europe, Estonia has seen a large epidemic since the 2000 s. It is almost the only European country that has epidemiological data on fentanyl use. In 2008, according to a national survey, the prevalence of fentanyl use in the general population (18–64 years old) was 0.1%. This proportion reached 1.1% among males aged 15 to 24. In 2011, the Estonian drug treatment database recorded 407 primary fentanyl/3methylfentanyl users among their 532 registered patients (EMCDDA, 2012). Users are predominantly injectors with a profile of social precariousness and from the Russian-speaking minority (EMCDDA, 2012). The particularity of Estonia is that fentanyls are mainly produced clandestinely inside the country.

In France, the latest report published by the French Monitoring Centre for Drugs and Drug Addiction stated that, between 2000 and 2017, 10 SOs were identified on the French territory: AH-7921 (notified in 2013), acetylfentanyl, despropiopyl-o-fluoro-fentanyl (reported in 2014), ocfentanyl, methylfentanyl, U-47,700, valerylfentanyl (reported in 2015), and W-15, metafluorofentanyl, furanylfentanyl (reported in 2016) (OFDT, 2017). In October 2015, the Regional Health Agency of Ile de France and the Paris Addictovigilance Center released an information note concerning an adulterated heroin product sold on the deep web. The analyses of 2 samples highlighted the presence of heroine (3% and 16%), acetaminophen (29% and 33%), caffeine (26% and 27%) and ocfentanyl (no information available concerning its purity) (ARS, 2015). In 2017, the French Agency for the Safety of Health Products initiated a survey to assess fentanyl use. The results have not yet been published. However, 16 intoxications with fentanyl analogues were reported to the French Addictovigilance Network between January 2012 and May 2017.

In Sweden, the use of fentanyl varies with the locality. Finland shares with its neighbor specific localizations of fentanyl use. While fentanyl analogues are not popular and little abused in the capital, other localities such as Turku are much more concerned. Indeed, according to a study on 200 drug users in Helsinki, only 2 people in precarious social situation reported using fentanyl. In another study based on the needle exchange program in Turku, 35% of the injectors admitted the use of fentanyl in the previous year. A survey on an opioid-substituted population in Turku reported that 30% reported fentanyl use in the previous year (EMCDDA, 2012). According to a study in 3 low-threshold services in Munich, 50% of respondents reported fentanyl use, mainly by intravenous route and mostly diverted from pharmaceutical patches (EMCDDA, 2012). Except for Germany and Estonia, diverted fentanyl is rare in the most of EU. Although precursors were seized in 1995, fentanyls are currently mainly diverted from pharmaceutical medicines.

National fentanyl seizures in the US increased by almost 400% from 2013 to 2014 and by almost 1400% from 2013 to 2015 (NFLIS, 2017). Between 2013 and 2015, the US law enforcement agency seized 239 kg of illicitly-produced fentanyls (DEA, 2016). In Europe, 60% of the 600 seizures of synthetic opioids in 2015 were fentanyls, accounting for 0.75% of all NPS seized and 0.04% of all quantities seized (EMCDDA, 2017b). The total quantity seized is small, but only a few micrograms are required to be active.

3. Clinical pharmacology

The effects of opioids derive directly from their pharmacological composition. Opioids bind to opioid receptors that are mainly present in the central and peripheral nervous system (Ghelardini et al., 2015). Up to seventeen opioid receptors have been reported, but three classes are the most important in humans: mu, kappa, and delta (Waldhoer et al., 2004). The mu-receptor class groups three subtypes: mu-1, mu-2, and mu-3. The effect of opioids depends on their affinity towards these different receptors, as well as on their pharmacodynamic properties and the localization of the receptors. In medical practice, opioids are prescribed for analgesia, and side-effects are well-known (Michna et al., 2014): tremor, paresthesia, dizziness, palpitations, heart rate and arterial pressure disorders, dyspnea, constipation, abdominal pain, nausea and vomiting, headache, allergic reactions, muscular contractions, and urinary retention. More rarely, convulsions and visual blur can occur. Psychiatric effects have been described, including agitation, dysphoria, hallucinations, disorientation, and confusion. The most dangerous side effect is respiratory depression (overdose).

The pharmacology of fentanyl and other prescribed medicines is well known (Janssen, 1982). Fentanyl, developed in 1959 by Jansen, is a complete mu receptor agonist 50–100 times more potent than morphine in animal studies. The onset of action and peak plasma concentration depend on the route of administration and the dose. The duration of action is about 2–4 hours after intravenous (IV) or transmucosal administration. Metabolization, mediated by the CYP450 isoenzyme system, produces inactive norfentanyl (Stanley, 2014). Extremely potent, only a small dose of fentanyl can induce intoxications and fatalities, the lethal dose being considered to be 2 mg for a non-opioid user (DEA, 2016). An Australian study in a Medically Supervised Injecting Center in Sydney showed that 4% of fentanyl injections were followed by overdose. They also estimated that fentanyl injections entailed approximately twice the risk of overdose compared to heroin injections and 8 times the risk of overdose compared to other prescription opioids such as oxycodone and morphine (Latimer et al., 2016).

Little is known about the pharmacological composition of other SOs. Many were synthesized in the 1970 s for medical purposes. A lot were never pursued as prescription medicines, among other things because of their addictive potency. It can be noted that no studies have evaluated their pharmacological and toxicological properties in humans (Lucyk and Nelson, 2017). Animal studies have indicated that most of them act on the mu opioid receptor. They can also act on the delta or kappa opioid receptors (Prekupec et al., 2017). Consequently, synthetic opioids generate similar effects to those that are sought with natural

opioids, such as drowsiness and short-term feelings of euphoria. According to experimental studies and user "trip" reports in forums, these effects are much more potent. Ocfentanyl is 100 times more potent than morphine in most animal models. Acetylfentanyl seems to be 15 times more potent (Rogers et al., 2016) and butyrylfentanyl 7 times more potent than morphine (Stanley, 2014) (Cole et al., 2015). Carfentanyl is currently the most powerful synthetic opioid : 10 000 times more potent than morphine with a much higher affinity for the mu receptor than for delta and kappa receptors (Zawilska, 2017). Regarding the "new generation" of SOs, no study assessing their pharmacological characteristics in humans is available. U-47,700 is a selective mu opioid agonist estimated to be 7–8 times more potent than morphine according to animal models (Mohr et al., 2016). AH-7921, detected in 2012 on the European drug market under the name of Doxylam, is a potent respiratory depressant acting as an agonist towards the mu opioid receptor and kappa opioid receptors at high doses. Its potency is similar to morphine. No studies are available in humans but users report a "narrow therapeutic window" between desired effects and intoxication symptoms (Zawilska, 2017) (Wohlfarth et al., 2016). MT-45 differs in that it acts on opioid (delta and kappa) and non-opioid receptors. The mechanism is still not well understood, but it could be responsible for the special effects reported, such as ototoxicity and profound loss of consciousness. Its potency is similar to that of morphine (Prekupec et al., 2017).

Little data on the pharmacokinetics of SOs are available. They have high lipophilicity so they quickly cross the blood-brain barrier and they have a large volume of distribution. The onset of action is fast (a few minutes), the duration of action is short (a few hours) and after-effects can last a few hours. The typical dose varies, depending on the substance, the route of administration and consumer habits (from 12.5 to 25 µg for insufflated acroylfentanyl to 45–60 mg for ingested MT-45) (Zawilska, 2017).

SOs are a challenge for clinicians but they are also a challenge for analysts. Products are highly concentrated in psychoactive substances and only small quantities are necessary to generate effects.

Although they share pharmacological properties with natural opioids, synthetic opioids are structurally different. As a result, routine urine drug tests cannot detect them yet. They are extremely potent, and only small quantities are necessary to obtain a result. Consequently, the detection of these substances and their metabolites can be difficult. In addition, the non-availability of analytical standards and cost are further limitations for the laboratories (CCENDU, 2015).

4. Complications of SO use

Acute and delayed toxic effects of these opioids have been reported, depending on the particular nature of the product.

4.1. Somatic complications

The fentanyl analogs have strong opioid receptor agonism. Fentanyl quickly crosses the blood–brain barrier as a result of its high lipid solubility, and has a rapid onset of action (approximately 2–5 min) (Helander et al., 2017a, b). Thus, the risk of overdose is very great because of both the rapid effect of the drug and the narrow therapeutic index (Zawilska, 2017). This index is narrower in patients with a long history of opioid use and a high tolerance level (Boyer, 2012).

SO intoxication is typically diagnosed on the basis of the patient's history, clinical presentation, or third party report. Providers and emergency physicians should keep in mind that common clinical signs include respiratory depression, cyanosis, myosis, central nervous system depression (drowsiness, coma and diminished consciousness), bradycardia, nausea, anxiety, and abdominal pain. However, as many symptoms are not specific, it may be difficult to differentiate these symptoms from poisoning from other sedative-hypnotic intoxications, particularly if several drugs have been co-ingested. Numerous specific clinical signs have been observed, varying with the opioid used. Fentanyl can cause chest wall rigidity and apnea, particularly following rapid intravenous administration (Suzuki and El-Haddad, 2017). Tachycardia has been observed with acetylfentanyl and 4-methoxybutyrfentanyl (4-MeO-butyrfentanyl) (Helander et al., 2016). Atypical characteristics during suspected fentanyl overdose included immediate blue discoloration of the lips, gurgling sounds with breathing, stiffening of the body or seizure-like activity, and foaming at the mouth, have been reported by third party observers (Somerville, 2017). Sedation and coma are known to be dose-related and depend on the route of administration.

Whereas the fentanyl analogs present the greatest risk for overdose, desomorphine intoxication is also devastating and entails serious complications for users (Florez et al., 2017). This drug has been popularized under the name of "Krokodil". The first addiction effects usually appear 5–10 days after intravenous or intramuscular injection and death comes at most after 2–3 years. It can cause allergic reactions, seizures, and respiratory depression leading to death (Florez et al., 2017). The specific effect of desomorphine is the inhibition of cholinesterase, which can result in a cholinergic syndrome including confusion and decreased consciousness, weakness, salivation, urinary and fecal incontinence, vomiting, sweating, muscle fasciculation, pulmonary edema, and seizures (Wright and Sabine, 1943)

Tramadol is an opioid-like analgesic that can be misused. Independently from the dose, it can cause seizures. A systematic screening of tramadol users or abusers admitted to hospital evaluated the frequency of seizures at 46% of cases (Talaie et al., 2009), ranging from abnormal signs on electroencephalography to generalized tonic-clonic seizures.

Adjuvants can also have their own specific effects and it can be very difficult to disentangle their effects from those of the drug, since the nature of the preparation is unknown. Some very damaging effects have been described for certain toxic or corrosive by-products and residuals of the manufacturing process of desomorphine as a result of inadequate purification (Grund et al., 2013). These symptoms involve discoloration and desquamation of the skin around the injection site, resembling the crocodile skin that has given its name to the product. This drug appears to be marketed only in Eastern Europe (Mullins and Schwarz, 2014). With continued use, gangrene and limb amputations can occur. The mixture can also cause venous damage, including ulcers and phlebitis around the injection sites (Lee and Ladizinski, 2014). But the damage is not limited to the injection sites, and distant organ damage has been reported, such as neurological, thyroid, hematological, liver and kidney lesions (Grund et al., 2013). Phosphorus adjuvants have been associated with osteonecrosis of the jaw (Poghosyan et al., 2014).

Loss and depigmentation of hair, discoloration of the nails, extensive folliculitis and dermatitis, elevated liver enzymes, bilateral hearing loss, eye irritation followed by severe bilateral secondary cataracts requiring surgery were all observed in a small sample of men after administration of MT-45 (Helander et al., 2017a,b). These symptoms were attributed to the presence of nitrogen mustards, reagents used in the synthesis of this product.

4.2. Psychiatric complications

The psychiatric effects of opioids depend on the localization of the receptors in the central nervous system (Ventura et al., 2018). Found in the spinal cord, the brainstem, and in the limbic and other diencephalic areas, the κ-receptors contribute to dysphoria. Euphoria seems to be related to the µ-opioid agonist effect in the brainstem and medial thalamus. The duration is variable and depends on the half-life of the drug (from 1 to 8 h). The psychiatric effects expected from opioid abuse are similar to those experienced with heroin: relaxation, a sense of well-being, and euphoria, often followed by a peaceful, dream-like state. Unwanted psychiatric effects include restlessness and anxiety, agitation, often occurring during withdrawal.

Table 1
classical and associated signs of opioid overdose.

Signs of opioid overdose
Classical signs ("triad")
• Respiratory depression
• Central nervous system depression (drowsiness, coma, confusion or low consciousness),
• Myosis
Associated signs (can be missing)
• Bradycardia
• Abdominal pain
• Nausea
• Hypothermia
• Cyanosis

A typology of overdose, based on semi-structured interviews undertaken with opiate users who had experienced a non-fatal overdose, has recently been proposed (Neale et al., 2017). Four types of overdose onset are distinguished: amnesic (no memory, rapid loss of consciousness and no description of the experience), conscious (some memory, sustained consciousness, feeling unwell with unpleasant symptoms), instant (some memory but rapid loss of consciousness) and enjoyable (some memory, pleasant or positive experience, rapid loss of consciousness) (Table 1).

Hallucinations and dissociations seem rare but have been reported. For example, hallucinations were reported with a homemade heroin substitute (Lemon, 2013). Other neuropsychiatric alterations have been reported consisting in motor, speech or memory impairments, and personality changes (Grund et al., 2013). MT-45 can generate dissociative-like symptoms (Helander et al., 2017a,b). A natural opioid, known as "magic mint", extracted from the plant Salvia divinorum (Lamiaceae), is a visual and auditory hallucinogenic psychoactive herb and has recently been used as a recreational drug (Sheffler and Roth, 2003). Its psychedelic effect is attributed to its kappa-opioid receptors antagonism.

Effect could also be related to individual factors, a phenomenon called idiosyncrasy (Uetrecht, 2007). Depending on their genetic background, their comorbidities or their previous exposure to drugs, users could have different individual reactions.

5. Fatalities

As early as 1991, Henderson reported 112 deaths related to fentantyl and analogues. For SOs other than methadone, overdose deaths increased by 265% between 2012 and 2015 and fatalities increased by 72% just between the years 2014 and 2015 (UNODC, 2017). In all, more than 5000 deaths caused by fentanyl and its analogues, have been recorded since 2013 (Green and Gilbert, 2016). In Canada, between 2009 and 2014, there were more than 655 fentanyl-implicated deaths and at least 1000 deaths where fentanyl was detected. More than half of them occurred in a mere 2-year period (2013–2014) These deaths were mainly localized in British Columbia, Alberta, Ontario and Quebec (CCENDU, 2015). In Australia, approximately 144 deaths related to fentanyl misuse were recorded between 2000 and 2012, mainly among young men (30–39 years old). Among them, 75% were unintentional. They were mainly caused by the injection of diverted pharmaceuticals (in particular after extraction from transdermal fentanyl patches) (NCIS, 2013) (Roxburgh et al., 2013).

In Estonia, Fentanyl and 3-methylfentanyl are the synthetic opioids the most commonly involved in deaths (UNODC, 2017) (Uuskula et al., 2015). About 1100 deaths were reported between 2005 and 2013, among which one hundred in recent years. In 2012, overdose mortality was around 11 times higher than the European average (Mounteney et al., 2015a,b). In France, 2 deaths were caused by ocfentanyl (ANSM, 2017). The first case is related to an injection of supposed heroine. Ocfentanil was titrated in the blood (3.7 ng/mL), in addition to ethanol, caffeine and acetaminophen. The second case showed a blood concentration of ocfentanyl at 11.6 ng/mL, in combination with 6-MAM and morphine (SFTA, 2017). In May 2017, the National Forensic Institute reported another case of fatality involving ocfentanyl (blood concentration 5.3 µg/L) in association with cannabis, cocaine, and MDMA, and a case series of 3 intoxications caused by nasal insufflation of capsules bought on the Darknet (blood concentrations varied from 13.9 to 35.2 µg/L, the capsules contained 17% of ocfentanyl) (INPS, 2017). In July 2017, the SFTA published guidelines for the conduct of toxicological analyses for deaths involving NPS. Among them, the basic list of synthetic opioids to look for is ocfentanil, carfentanil, furanylfentanyl, metafluorofentanyl, U-47,700, acryloylfentanyl, and desomorphine (SFTA, 2017). In Sweden, the first fentanyl-related deaths were recorded in 1994 (Kronstrand et al., 1997). Between 2006 and 2013, 180 fentanyl-related deaths were recorded (Mounteney et al., 2015a,b). Between 2015 and 2016, 7 fatalities related to furanylfentanyl (alone or in combination with other drugs) were added (Guerrieri et al., 2017). In 2016, 39 fatal intoxications (among which 21 between March and August) related to acryloylfentanyl were reported to the EMCDDA (EMCDDA, 2017a). Concerning the new synthetic opioids, which are not related to the fentanyl structure, intoxications and deaths have also been reported, including AH7921 and MT-45 (Zawilska and Andrzejczak, 2015; EMCDDA, 2017a). Deaths were also reported in Finland with 40 cases related to fentanyl between 2008 and 2010 and 4 other cases related to U-47,700 in 2016 (EMCDDA, 2017a) (Mounteney et al., 2015a,b). Germany particularly has seen increasing fatalities among injectors since 2007. In all, 160 fatal cases were reported between 2007 and 2011, particularly in Bavaria (EMCDDA, 2012).

The first European fentanyl death caused by adulterated cocaine was reported in Italy in 1992 (Ferrara et al., 1994). Between 2007 and 2012, 70 deaths related to fentanyl were reported in the UK, and 5 deaths in Greece during the period 2005–2011 (Mounteney et al., 2015a, b). In Belgium, a case of fatal intoxication with snorted ocfentanyl was published in 2016 (Coopman et al., 2016). 4-fluorobutyrylfentanyl was analytically confirmed to be the cause of 2 deaths in Poland (Rojkiewicz et al., 2017). In Russia, at least 12 deaths involving acetylfentanyl have been recorded since 2012 (Zawilska and Andrzejczak, 2015) but the well known 172 fentanyl-related deaths could have resulted from the military use of gas/aerosols of supposed fentanyl derivatives remifentanyl and carfentanyl to incapacitate terrorists in a Moscow theater in 2002 (Riches et al., 2012).

6. Therapeutic approach

6.1. Management of SO intoxication

Different clinical profiles are observed in SO overdose with respect to pharmacokinetics and potency compared to morphine.

Emergency physicians are on the front line to deal with opioid overdose. Emergency management is indicated as soon as possible, given the high potency of SOs, the rapid onset of effects and the short duration of action (Vuckovic et al., 2009). As previously seen, SO intoxication has common clinical signs and unspecific symptoms.

The management of SO intoxication includes airway support and administration of opioid antagonists to reverse respiratory depression. Intoxications of this sort can be potentially life-threatening unless treated early with the mu-receptor antagonist naloxone. Naloxone should be administered as soon as possible to reverse the typical opioid symptoms, for its ability to rapidly reverse the clinical signs of opioid overdose, and life-threatening respiratory depression (Zawilska, 2017). Naloxone is a short-acting semisynthetic competitive opioid receptor antagonist with the highest affinity for the mu receptor. The drug can be administered by intravenous, intramuscular, subcutaneous, and intranasal routes. Whatever the suspected route of ingestion of the opioids, the effective dose of naloxone that should be administered is

not known. Titration is the rule to avoid precipitating opioid withdrawal symptoms. The dose given depends on the patient's weight, the supposed ingested dose of NPS and the relative binding affinities to the mu-receptor. An initial dose of 0.4 mg is given intravenously and multiple doses of naloxone may be needed when seeking to reverse drug overdoses due to long-standing opioid use. If the intravenous route is not possible, intramuscular or subcutaneous administration should be considered. Intranasal delivery may require a higher dose of 4 mg. After administration of naloxone, response can be seen within two minutes if administered intravenously, and typically within 10 min if administered intranasally or intramuscularly. The dose can be repeated at 2–3-min intervals until the patient is breathing at a rate greater than 10 breaths/minute. A number of articles suggest that intranasal naloxone has a strong evidence base as a first-line therapy for people with suspected opioid overdose in the prehospital setting. Although the time required to reverse opioid overdose is longer compared to intravenous administration, the overall time between the arrival of rescue and clinical response seems similar between intranasal and intravenous routes taking account of the time required to insert an intravenous line (Merlin et al., 2010).

6.2. How long should the patient be observed in the emergency department?

This question is still debated. In case of repeat administration of naloxone, some authors assert that the patient should be observed for at least 2 h after reversal of respiratory depression.

Given that the duration of action of naloxone is only 30–120 minutes, repeat dosing may be required, especially in large opioid overdoses. Depending on the drug taken, larger doses (up to 10 mg) of naloxone can be required. Patients who require multiple naloxone doses should be considered for admission to Emergency department. An opioid overdose patient should be monitored for at least 2 h after reversal of respiratory depression. In addition, patients with substance abuse disorders can have the benefit of screening and counseling while under observation for detoxification in ED, which is particularly important if they are not in contact with primary care. One difficulty that can arise during the period of observation is that these patients frequently desire to leave the Emergency Department shortly or immediately after reversal under naloxone.

6.3. Prevention

Emergency physicians and the public should be aware of the rapidly increasing incidence and severity of toxicity from illicit opioids. The time of observation in the emergency department can often reveal the past history of the patient, the type of drug taken and create a contact with primary care. A brief face-to-face intervention is easy to perform in the emergency department while patients are waiting for the results of their extensive investigations in order to plan a follow-up after the patient is discharged.

Measures to control many of these substances should continue, despite the fact that they are continuously modified to avoid existing laws.

An efficient approach entails a focus on the patient, and harm reduction programs that provide prescription naloxone coupled with education and training enabling intravenous drug users to reverse accidental overdoses. Currently, there is a need to increase the availability of naloxone for opioid users. Several countries have implemented programs. For example, in some jurisdictions, police officers and emergency services can administer naloxone if other medical personnel are not on-scene (Willman et al., 2017). In the context of the increased potency of synthetic opioids, it is essential to make it easier to administer intranasal naloxone through a drug/device combination product that is easy to use and effective, and to ensure that the route of administration is safe.

Conflict of interest

Laurent Karila receives consulting fees from Sanofi Aventis, Gillead, Eutherapie, Bouchara-Recordati, Jansse-Cilag, Takeda, DA Pharmaceuticals.

Amine Benyamina has received consulting fees from Bristol-Myers-Squibb, Lundbeck, Merck-Serono and Mylan Pharmaceuticals. He is an Indivior pharmaceuticals scientific board member.

Nicolas Franchitto has received sponsorship to attend scientific meetings from Lundbeck and Indivior.

Maude Marillier, Joël Billieux, and Boris Chaumette have no conflict of interest.

References

ANSM, 2017. Agence Nationale de Sécurité des Médicaments et des Produits de Santé (ANSM). Commission des stupéfiants et psychotropes: Compte rendu de la séance du 12 janvier 2017. Available from:. http://ansm.sante.fr/var/ansm_site/storage/original/application/3805df37cf2cd7bb99fbcc8c17e.pdf.

Arens, A.M., van Wijk, X.M., Vo, K.T., Lynch, K.L., Wu, A.H., Smollin, C.G., 2016. Adverse effects from counterfeit alprazolam tablets. JAMA Intern. Med. 176 (10), 1554–1555.

ARS, 2015. Agence Régionale de Santé Ile de France. Note d'information: Circulation sur le Deep Web d'héroïne coupée à l'ocfentanil (2015). .

Boyer, E.W., 2012. Management of opioid analgesic overdose. N. Engl. J. Med. 367 (2), 146–155. %U. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3739053/.

CCENDU, 2015. Canadian Community Epidemiology Network on Drug Use. CCENDU Bulletin: Deaths Involving Fentanyl in Canada (2009–2014). Canadian Centre on Substance Abuse, Ottawa, Ont.

Cole, J.B., Dunbar, J.F., McIntire, S.A., Regelmann, W.E., Slusher, T.M., 2015. Butyrfentanyl overdose resulting in diffuse alveolar hemorrhage. Pediatrics 135 (3), e740-743.

Coopman, V., Cordonnier, J., de Leeuw, M., Cirimele, V., 2016. Ocfentenil overdose fatality in the recreational drug scene. Forensic Sci. Int. 266, 469–473.

Coppola, M., Mondola, R., 2015. AH-7921: a new synthetic opioid of abuse. Drug. Alcohol. Rev. 34 (1), 109–110.

DEA, 2015. U.S. Department of Justice Drug Enforcement Administration. DEA Issues Nationwide Alert on Fentanyl as Threat to Health and Public Safety (2015). Available from:. https://www.dea.gov/divisions/hq/2015/hq031815.shtml.

DEA, 2016. U.S. Department of Justice Drug Enforcement Administration. Counterfeit Prescription Pills Containing Fentanyls: A Global Threat (2016). Available from:. . https://content.govdelivery.com/attachments/USDOJDEA/2016/07/22/file_attachments/590360/fentanyl%2Bpills%2Breport.pdf.

EMCDDA, 2012. Fentanyl in Europe, EMCDDA Trendspotter Study Report. Publications Office for the European Union, Luxembourg.

EMCDDA, 2017a. European Monitoring Centre for Drugs and Drug Addiction. High-Risk Drug Use and New Psychoactive Substances, EMCDDA Rapid Communication. Publications Office of the European Union, Luxembourg.

EMCDDA, 2017b. European Drug Report 2017: Trends and Developments. Publications Office of the European Union, Luxembourg.

Ferrara, S., Snenghi, R., Tedeschi, L., 1994. Fatality due to fentanyl-cocaine intoxication resulting in a fall. Int. J. Legal Med. 106 (5), 271–273.

Florez, D.H.Â., Dos Santos Moreira, A.M., da Silva, P.R., Brandão, R., Borges, M.M.C., de Santana, F.J.M., Borges, K.B., 2017. Desomorphine (Krokodil): an overview of its chemistry, pharmacology, metabolism, toxicology and analysis. Drug Alcohol Depend. 173, 59–68.

Ghelardini, C., Di Cesare Mannelli, L., Bianchi, E., 2015. The pharmacological basis of opioids. Clin. Cases Min. Bone Metab. 12 (3), 219–221.

Green, T., Gilbert, M., 2016. Counterfeit medications and fentanyl. JAMA Intern. Med. 176 (10), 1555–1557.

Grund, J.-P.C., Latypov, A., Harris, M., 2013. Breaking worse: the emergence of krokodil and excessive injuries among people who inject drugs in Eurasia. Int. J. Drug. Policy 24 (4), 265–274.

Guerrieri, D., Rapp, E., Roman, M., Druid, H., Kronstrand, R., 2017. Postmortem and toxicological findings in a series of furanylfentanyl-related deaths. J. Anal. Toxicol. 41 (3), 242–249.

Helander, A., Backberg, M., Beck, O., 2016. Intoxications involving the fentanyl analogs acetylfentanyl, 4-methoxybutyrfentanyl and furanylfentanyl: results from the Swedish STRIDA project. Clin. Toxicol. (Phila.) 54 (4), 324–332.

Helander, A., Bäckberg, M., Signell, P., Beck, O., 2017a. Intoxications involving acrylfentanyl and other novel designer fentanyls – results from the Swedish STRIDA project. Clin. Toxicol. 55 (6), 589–599 %U https://doi.org/510.1080/15563650.15562017.11303141.

Helander, A., Bradley, M., Hasselblad, A., Norlén, L., Vassilaki, I., Bäckberg, M., Lapins, J., 2017b. Acute skin and hair symptoms followed by severe, delayed eye complications in subjects using the synthetic opioid MT-45. Br. J. Dermatol. 176 (4), 1021–1027.

Henderson, G., 1991. Fentanyl-related deaths: demographics, circumstances, and toxicology of 112 cases. J. Forensic Sci. 36 (2), 422–433.

INPS (2017). Marchard A., Martin-Molins C., Moal A., Vieira P., Sibille P., Milan N.L.,' Ocfentanil, un bon exemple des dangers des NPS (New Psychoactive Substances). Poster at French Society of Analytical Toxicology Congress, May 2017.

Janssen, P., 1982. Potent, new analgesics, tailor-made for different purposes. Acta Anaesthesiol. Scand. 26 (3), 262–268.
Klar, S.A., Brodkin, E., Gibson, E., Padhi, S., Predy, C., Green, C., Lee, V., 2016. Notes from the Field: furanyl-fentanyl overdose events caused by smoking contaminated crack cocaine - British Columbia, Canada, July 15–18, 2016. MMWR Morb. Mortal. Wkly. Rep. 65 (37), 1015–1016.
Kronstrand, R., Druid, H., Holmgren, P., Rajs, J., 1997. A cluster of fentanyl-related deaths among drug addicts in Sweden. Forensic Sci. Int. 88 (3), 185–193.
Latimer, J., Ling, S., Flaherty, I., Jauncey, M., Salmon, A.M., 2016. Risk of fentanyl overdose among clients of the Sydney medically supervised injecting Centre. Int. J. Drug. Policy 37, 111–114.
Lee, K.C., Ladizinski, B., 2014. Mucocutaneous manifestations of illicit drug use. Int. J. Dermatol. 53 (8), 1048–1051.
Lemon, T.I., 2013. Homemade heroin substitute causing hallucinations. Afr. J. Psychiatry 16 (6).
Lucyk, S., Nelson, L., 2017. Novel synthetic opioids: an opioid epidemic within an opioid epidemic. Ann. Emerg. Med. 69 (1), 91–93.
Madras, B.K., 2017. The growing problem of new psychoactive substances (NPS). Curr. Top. Behav. Neurosci. 32, 1–18.
Merlin, M.A., Saybolt, M., Kapitanyan, R., Alter, S.M., Jeges, J., Liu, J., Calabrese, S., Rynn, K.O., Perritt, R., Pryor 2nd, P.W., 2010. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am. J. Emerg. Med. 28 (3), 296–303.
Michna, E., Cheng, W.Y., Korves, C., Birnbaum, H., Andrews, R., Zhou, Z., Joshi, A.V., Schaaf, D., Mardekian, J., Sheng, M., 2014. Systematic literature review and meta-analysis of the efficacy and safety of prescription opioids, including abuse-deterrent formulations, in non-cancer pain management. Pain Med. (Malden, Mass.) 15 (1), 79–92.
Mohr, A.L., Friscia, M., Papsun, D., Kacinko, S.L., Buzby, D., Logan, B.K., 2016. Analysis of novel synthetic opioids u-47700, U-50488 and furanyl fentanyl by LC-MS/MS in postmortem casework. J. Anal. Toxicol. 40 (9), 709–717.
Mounteney, J., Giraudon, I., Denissov, G., Griffiths, P., 2015a. Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. Int. J. Drug. Policy 26 (7), 626–631.
Mounteney, J., Giraudon, I., Denissov, G., Griffiths, P., 2015b. Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. Int. J. Drug. Policy. 26 (7), 626–631.
Mullins, M.E., Schwarz, E.S., 2014. 'Krokodil' in the United States is an urban legend and not a medical fact. Am. J. Med. 127 (7), e25.
NCIS, 2013. National Coronial Information System. Deaths Related to Fentanyl Misuse – An Update (July 2000–December 2012) (2013). Available from:. http://www.ncis.org.au/wp-content/uploads/2013/11/Fentanyl-fact-sheet-Australian-data-only-October-2013.pdf.
NDEWS, 2015. National Drug EarlyWarning System (NDEWS). NDEWS Special Reports. Available from:. Fentanyl and Fentanyl Analogs. http://pub.lucidpress.com/NDEWSFentanyl/.
Neale, J., Bradford, J., Strang, J., 2017. Development of a proto-typology of opiate overdose onset. Addiction (Abingdon, Engl.) 112 (1), 168–175.
NFLIS, 2017. U.S. Drug Enforcement Administration, Diversion Control Division. NFLIS Brief: Fentanyl, 2001-2015. U.S. Drug Enforcement Administration, Springfield, VA.
NIDA/NIH, 2016. National Institute on Drug Abuse. Available from:. National Institutes of Health; U.S. Department of Health and Human Services. Drug Facts, Fentanyl. https://www.drugabuse.gov/publications/drugfacts/fentanyl.
OFDT, 2017. Synthèse thématique : nouveaux produits de synthèse. Available from:. https://www.ofdt.fr/produits-et-addictions/de-z/nouveaux-produits-de-synthese/.
Poghosyan, Y.M., Hakobyan, K.A., Poghosyan, A.Y., Avetisyan, E.K., 2014. Surgical treatment of jaw osteonecrosis in "Krokodil" drug addicted patients. J. Cranio-Maxillo-Facial Surg. 42 (8), 1639–1643.
Prekupec, M.P., Mansky, P.A., Baumann, M.H., 2017. Misuse of novel synthetic opioids: a deadly new trend. J. Addict. Med. 11 (4), 256–265.
Quintana, P., Ventura, M., Grifell, M., Palma, A., Galindo, L., Fornis, I., Gil, C., Carbon, X., Caudevilla, F., Farre, M., Torrens, M., 2017. The hidden web and the fentanyl problem: detection of ocfentanil as an adulterant in heroin. Int. J. Drug. Policy 40, 78–83.
Riches, J.R., Read, R.W., Black, R.M., Cooper, N.J., Timperley, C.M., 2012. Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentanil and remifentanil use. J. Anal. Toxicol. 36 (9), 647–656.
Rogers, J.S., Rehrer, S.J., Hoot, N.R., 2016. Acetylfentanyl: an emerging drug of abuse. J. Emerg. Med. 50 (3), 433–436.
Rojkiewicz, M., Majchrzak, M., Celiński, R., Kuś, P., Sajewicz, M., 2017. Identification and physicochemical characterization of 4-fluorobutyrfentanyl (1-((4-fluorophenyl)(1-phenethylpiperidin-4-yl)amino)butan-1-one, 4-FBF) in seized materials and post-mortem biological samples. Drug. Test. Anal. 9 (3), 405–414.
Roxburgh, A., Burns, L., Drummer, O.H., Pilgrim, J., Farrell, M., Degenhardt, L., 2013. Trends in fentanyl prescriptions and fentanyl-related mortality in Australia. Drug. Alcohol. Rev. 32 (3), 269–275.
SFTA, 2017. French Society of Analytical Toxicology. SFTA Guidelines for the Achievement of Toxicological Analyzes for Deaths Involving NPS. Available from:. http://sfta.org/img/uploads/2017/07/RecoSFTApourRCMavecNPS.pdf.
Sheffler, D.J., Roth, B.L., 2003. Salvinorin a: the "magic mint" hallucinogen finds a molecular target in the kappa opioid receptor. Trends Pharmacol. Sci. 24 (3), 107–109.
Somerville, N., 2017. Characteristics of Fentanyl Overdose - Massachusetts, 2014-2016. MMWR Morb Mortal Wkly Rep. [Internet]. 2017 [cited 2017 Sep 8];66. Available from:. https://www.facebook.com/CDCMMWR.
Stanley, T., 2014. The fentanyl story. J. Pain. 15 (12), 1215–1226.
Sutter, M.E., Gerona, R.R., Davis, M.T., Roche, B.M., Colby, D.K., Chenoweth, J.A., Adams, A.J., Owen, K.P., Ford, J.B., Black, H.B., Albertson, T.E., 2017. Fatal fentanyl: one pill can kill. Acad. Emerg. Med. 24 (1), 106–113.
Suzuki, J., El-Haddad, S., 2017. A review: fentanyl and non-pharmaceutical Fentanyls. Drug. Alcohol. Depend. 171, 107–116.
Talaie, H., Panahandeh, R., Fayaznouri, M., Asadi, Z., Abdollahi, M., 2009. Dose-independent occurrence of seizure with tramadol. J. Med. Toxicol. 5 (2), 63–67.
Uetrecht, J., 2007. Idiosyncratic drug reactions: current understanding. Annu. Rev. Pharmacol. Toxicol. 47, 513–539.
UNODC, 2017. United Nations Office on Drugs and Crime, World Drug Report 2017. (ISBN: 978-92-1-148291-1, eISBN: 978-92-1-060623-3, United Nations Publication, Sales No. E.17.XI.6).
Uuskula, A., Raag, M., Vorobjov, S., Ruutel, K., Lyubimova, A., Levina, O.S., Heimer, R., 2015. Non-fatal overdoses and related risk factors among people who inject drugs in St. Petersburg, Russia and Kohtla-Jarve, Estonia. BMC Public Health 15, 1255.
Ventura, L., Carvalho, F., Dinis-Oliveira, R.J., 2018. Opioids in the frame of new psychoactive substances network: a complex pharmacological and toxicological issue. Curr. Mol. Pharmacol. 11 (2), 97–108.
Vuckovic, S., Prostran, M., Ivanovic, M., Dosen-Micovic, L., Todorovic, Z., Nesic, Z., Stojanovic, R., Divac, N., Mikovic, Z., 2009. Fentanyl analogs: structure-activity-relationship study. Curr. Med. Chem. 16 (19), 2468–2474.
Waldhoer, M. S., Bartlett, E., and J., Whistler, L., (2004). Opioid Receptors." Annual Review of Biochemistry 73(1): 953-990 %U https://doi.org/910.1146/annurev.biochem.1173.011303.073940.
Willman, M.W., Liss, D.B., Schwarz, E.S., Mullins, M.E., 2017. Do Heroin overdose patients require observation after receiving naloxone? Clin. Toxicol. (Phila.) 55 (2), 81–87.
Wohlfarth, A., Scheidweiler, K., Pang, S., Zhu, M., Castaneto, M., Kronstrand, R., Huestis, M., 2016. Metabolic characterization of AH-7921, a synthetic opioid designer drug: in vitro metabolic stability assessment and metabolite identification, evaluation of in silico prediction, and in vivo confirmation. Drug. Test. Anal. 8 (8), 779–791.
Wright, C.I., Sabine, J.C., 1943. The inactivation of cholinesterase by morphine, dilaudid, codeine and desomorphine. J. Pharmacol. Exp. Ther. 78 (4), 375–385. %* © 1943 % U. http://jpet.aspetjournals.org/content/1978/1944/1375.
Zawilska, J.B., 2017. An expanding world of novel psychoactive substances: opioids. Front. Psychiatry 8, 110.
Zawilska, J.B., Andrzejczak, D., 2015. Next generation of novel psychoactive substances on the horizon - a complex problem to face. Drug Alcohol. Depend. 157, 1–17.