Drug and Alcohol Dependence 171 (2017) 107–116

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Review

A review: Fentanyl and non-pharmaceutical fentanyls

Joji Suzuki[a,b,c,*], Saria El-Haddad[a,b,c]

[a] Brigham and Women's Hospital, 60 Fenwood Rd., Boston, MA 02115, United States
[b] Brigham and Women's Faulkner Hospital, 1153 Centre St., Boston, MA 02130, United States
[c] Harvard Medical School, 25 Shattuck St., Boston, MA 02115, United States

ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form
22 November 2016
Accepted 24 November 2016
Available online 16 December 2016

Keywords:
Fentanyl
Non-pharmaceutical fentanyl
Overdose
Opioid use disorder

ABSTRACT

Background: Fentanyl and non-pharmaceutical fentanyls (NPFs) have been responsible for numerous outbreaks of overdoses all over the United States since the 1970s. However, there has been a growing concern in recent years that NPFs are contributing to an alarming rise in the number of opioid-related overdoses.
Methods: The authors conducted a narrative review of the published and grey literature on fentanyl and NPFs in PubMed, Google Scholar, and Google using the following search terms: "fentanyl", "non-pharmaceutical fentanyl", "fentanyl analogs", "fentanyl laced heroin" and "fentanyl overdose". References from relevant publications and grey literature were also reviewed to identify additional citations for inclusion.
Results: The article reviews the emergence and misuse of fentanyl and NPFs, their clinical pharmacology, and the clinical management and prevention of fentanyl-related overdoses.
Conclusions: Fentanyl and NPFs may be contributing to the recent rise in overdose deaths in the United States. There is an urgent need to educate clinicians, researchers, and patients about this public health threat.

1. Introduction

In 2014, over 10 million individuals in the United States reported the use of illicit opioids as well as prescription opioids for non-medical reasons, contributing to drug-related overdose deaths which now outnumber traffic fatalities (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014. Despite the concerted efforts to address the opioid crisis in this country, in recent years there has been a dramatic increase in overdoses from synthetic opioids, specifically fentanyl and related analogs (Drug Enforcement Administration (DEA); Rudd et al., 2016; Spies et al., 2016). From 2013 to 2014, the age-adjusted death rate from heroin, semi-synthetic opioids (i.e., oxycodone, hydrocodone), and synthetic opioids other than methadone increased by 26%, 9%, and 80%, respectively (Rudd et al., 2016). Evidence is now accumulating that drug manufacturers and dealers may be adding illicitly produced non-pharmaceutical fentanyl (NPF) to increase the potency of their products (Gladden et al., 2016; Hempstead and Yildirim, 2013; Peterson et al., 2016). While some individuals are using fentanyl and NPFs unintentionally through the use of fentanyl-laced heroin, others are knowingly seeking out fentanyl containing products due to the perception they are more desirable (Fernando, 1991; Mars et al., 2015).

The true extent of the illicit fentanyl and NPF use in the general population is difficult to ascertain, because routine toxicology screens will not detect synthetic opioids that have little structural homology to morphine and other commonly tested opioids. Nevertheless, fentanyl-related ED visits in the US increased from 9823 in 2004 to 20,034 in 2011, representing an increase of 104% (SAMHSA, 2013). At the same time, reports on state drug seizures from the National Forensic Laboratory Information System, a program of the (DEA, 2015a) office of diversion control, have noted an increase of fentanyl seizures by 259% from the second half of 2013 to the first half of 2014 (Centers for Disease Control and Prevention, 2015; DEA, 2015b). Fentanyl-related overdoses in Ohio, for example, increased from 84 in 2013 to 502 in 2014 (Spies et al., 2016). In Massachusetts, among the 1319 opioid-related death where toxicology results were available in 2015, 754 (57%) tested positive for fentanyl (Massachusetts Department of Public Health, 2016). Given the public health importance of this emerging problem, the aim of this review is to summarize the use and misuse of pharmaceutical fentanyl, clinical pharmacology of fentanyl, review of NPFs, and clinical management and prevention of fentanyl related overdoses.

* Corresponding author at: Department of Psychiatry, Brigham and Women's Hospital, 60 Fenwood Rd., Boston, MA 02115, United States.
E-mail address: jsuzuki2@partners.org (J. Suzuki).

http://dx.doi.org/10.1016/j.drugalcdep.2016.11.033
0376-8716/

2. The use and misuse of pharmaceutical fentanyl

For at least several thousand years, *papaver somniferum* has been cultivated by humans to harvest opium for its analgesic and medicinal properties. In the early 19th century, both morphine and codeine were isolated from opium, heralding an era of using pure alkoloids isolated from medicinal plants. From these starting materials, referred to as opiates, a variety of semi-synthetic opioids were created, including diacetyl-morphine (heroin) and oxycodone. In 1937, German scientists looking for an anticholinergic agent discovered that meperidine, a chemical that is structurally unrelated to the opiates, had substantial analgesic properties similar to morphine. The discovery of synthetic opioids eventually led to the development of methadone in 1939. Subsequently, fentanyl was developed in 1960 by Paul Janssen in Belgium and introduced into clinical medicine in Europe (Stanley, 2014). At the time, fentanyl was the fastest acting and most potent opioid ever discovered, about 50–100 times more potent than morphine (Poklis, 1995). Fentanyl was introduced to the United States in the early 1970s under the trade name Sublimaze® as an intravenous anesthetic. Fentanyl quickly emerged as an important intravenous anesthetic agent, first used in combination with droperidol, but later as a single agent anesthetic. Morphine had already been identified as an effective anesthetic agent in the 1970s, but problems with awareness during surgery and hypertension made it problematic (Stanley, 2014). Fentanyl was found to be superior, given its higher potency, shorter onset, duration of action, absence of histamine release or venodilation, less hypotension and hypertension, and a faster recovery from anesthesia after extubation (Stanley, 1992). Another advantage of fentanyl is the cheaper production costs due to the reliance on readily available synthetic precursors, compared to the costlier method of extracting morphine from cultivated opium poppies.

The clinical success of fentanyl as an anesthetic fueled the dramatic rise in its popularity and sales. Within a year of going off patent, sales increased by 10-fold in the United States (Stanley, 2014). Subsequently, various analogues and novel delivery methods were investigated, leading to the introduction of sufentanil, alfentanil, lofentanil and remifentanil (see Table 1). In addition to its utility in humans, fentanyl analogues, such as carfentanil, became useful in veterinary medicine for rapid immobilization of wild animals (De Vos, 1978). By the mid-1980s, transdermal formulations and other routes of administration were being tested for the treatment of severe pain in opioid tolerant patients, eventually making fentanyl and related analogs the most widely used synthetic opioids in clinical practice (Stanley, 2014).

However, by four years after approving the transdermal patch in 1994, the FDA issued a formal warning concerning the dangers of fentanyl patches given the growing number of reports of accidental overdoses, and reiterated the need to prescribe these medications only to those with severe pain that cannot be managed with less powerful opioids or to those with an established tolerance to opioids (Wyman, 1994) Fentanyl patches are contraindicated in the treatment of post-operative and acute pain in patients who are opioid naive and are expected to require only a short course of treatment (Janssen Pharmaceutica Products, 2003). Users must be cautioned about avoiding applying any heat sources to the patch, such as heating pads or electric blankets, which can increase the release and absorption of fentanyl through the skin.

Given the ongoing reports of unintentional overuse of patches, the FDA issued additional warnings in 2005 and 2007 to warn prescribers about the dangers of this medication (Biedrzycki et al., 2009; Edinboro et al., 1997; Food and Drug Administration, 2005, 2007; Kramer and Tawney, 1998). Recent data suggest that many patients may still be receiving fentanyl products inappropriately, despite these repeated warnings (Friesen et al., 2016). In a study of 11,000 patients in Manitoba, Canada newly initiated on fentanyl between 2001 and 2013, fentanyl initiation was deemed unsafe in the majority (74%) of patients due to inadequate opioid tolerance prior to initiation (Friesen et al., 2016).

With the increasing availability and popularity of fentanyl in surgery, the intentional misuse of pharmaceutical fentanyl started to be reported in the 1980s, with a focus on anesthesiologists and surgeons who were at particular risk presumably from having occupational exposure and easy access (Garriott et al., 1984; Pare et al., 1987; Silsby et al., 1984). In the first report describing health care providers dependent on fentanyl, 3 were anesthesiologists, and 3 were nurse anesthetists (Silsby et al., 1984). In a survey of anesthesiology training programs in the US encompassing the period between 1970 and 1980, training directors reported a 1.3% incidence of drug misuse (Ward et al., 1983). Meperidine was identified as the most commonly misused drug, followed by fentanyl, morphine, and then diazepam. Similarly, in a survey of 116 oral and maxillofacial surgery training programs, both meperidine and fentanyl were the most commonly misused drugs among their trainees discovered to be impaired from drug use (Rosenberg, 1986). Even though alcohol remains the most commonly used substance, fentanyl and sufentanil continue to be the most commonly misused drugs among anesthesiologists (Bryson and Silverstein, 2008; Jungerman et al., 2012; Kintz et al., 2005).

Reports continued to accumulate throughout the 1990s and 2000s regarding the misuse of pharmaceutical fentanyl products, notable for reports of fentanyl overdoses by health care providers or hospital staff (Chaturvedi et al., 1990; Levine et al., 1990; Matejczyk, 1988; Pare et al., 1987), and intentional misuse of patches by oral use, injection or inhalation (Lilleng et al., 2004; Marquardt and Tharratt, 1994; Reeves and Ginifer, 2002; Tharp et al., 2004; Woodall et al., 2008). The intentional misuse of pharmaceutical fentanyl products has not appeared commonly outside of medical settings. However, this may be changing given there are now reports of numerous overdoses from those using heroin laced with carfentanil, a veterinary drug used to immobilize large animals but not approved for human use (Franko, 2016; WKRC, 2016). It remains to be seen if the carfentanil was diverted from legitimate supplies, produced illicitly, or purchased from overseas.

3. Clinical pharmacology of fentanyl

Fentanyl is a full agonist at the mu-opioid receptor, and approximately 50–100 times more potent than morphine. Because fentanyl and NPFs are active in the sub–100 μg range, they are some of the most potent medications known to exist. Similar to other opioid agonists, fentanyl's effects include analgesia, anxiolysis, euphoria, drowsiness, feelings of relaxation, respiratory depression, constipation, miosis, nausea, pruritus, and cough suppression, but also orthostatic hypotension, urinary urgency or retention, postural syncope and chest wall rigidity especially with IV use (Coruh et al., 2013; Janssen Pharmaceutica Products, 2003). The high lipophilicity of fentanyl and NPFs enables rapid diffusion through membranes including the blood brain barrier and lipid-rich compartments (Hug and Murphy, 1979). Subjective effects can be felt within one circulation time after injection use, and can produce analgesia and unconsciousness within minutes (Poklis, 1995). Respiratory depression is maximal at 2–5 min after a single IV dose administration, and some level of persistent respiratory depression is evident even after 2–3 h (Harper et al., 1976; McClain and Hug, 1980). The rapid uptake of fentanyl into tissues leads to a rapid fall in serum levels, with 98.6% of the dose eliminated from plasma within 60 min, with an elimination half-life of 219 min (McClain and Hug, 1980). The subsequent slow re-distribution from fatty tissues back into plasma likely explains the prolonged elimi-