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Abuse potential of fentanyl and fentanyl analogues

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Abstract

Introduction: In this perspective review, we evaluated the clinical management of fatal fentanyl overdose in several routes of administration, concentrating on both legally prescribed and illegally produced formulations.

Methods: A literature search was conducted on Web of Science, PubMed, and Google Scholar databases, using the following keywords: fentanyl, illicit fentanyl, deaths, misuse, abuse, and naloxone. We included only articles whose abstracts were available in English. All articles were screened using their abstracts to determine their relevance to the current review.

Results: The gold standard for treating both acute and chronic pain is fentanyl, but abuse of the drug has exploded globally since the late 2000s. Fentanyl abuse has been shown to frequently result in serious harm and even death.

Conclusions: By educating patients and physicians, making rescue kits easily accessible, developing vaccines to prevent opioid addiction, and perhaps even creating new tamper-resistant fentanyl formulations, it may be possible to prevent fentanyl misuse, therapeutic errors, and the repercussions that follow.

Opioid crisis

The opioid crisis in the United States is a public health epidemic. It claimed 932,000 lives since 1999. Of these fatalities, 263,000 died using prescription opioids. Since 1999, there has been an exponential increase in overdose deaths caused by heroin, fentanyl, and a variety of low-cost synthetic fentanyl analogs. This increase has been described as a triple-wave phenomenon that includes prescription opioids (1999-2010), heroin (2010-2017), and fentanyl (and its analogs), which are responsible for the current hike. Fentanyl overdose caused 9,945 deaths in 2016, but the death toll spiked to 20,145 in the first half of 2017.[1,2] According to the Centers for Disease Control and Prevention,[3] opioid overdose deaths increased through 2020, rising from 68,630 in 2020 to 107,000 in 2021. Fentanyl and synthetic opioid overdoses rose from 56,516 to 71,238 in 2021.[4]

Fentanyl accounts for over 68% of fatal overdoses caused by synthetic opioids. Fentanyl – as well as its analogs carfentanil, sufentanil, and alfentanil – are relatively novel synthetic opioids on the rise in both commercially regulated and illicit drug markets. During the COVID-19 pandemic, the percentage of individuals who tested positive for illicitly manufactured fentanyl and heroin rose by 35% and 44%, respectively. Age-adjusted drug overdose deaths in the United States increased 31% from 2019 to 2020.[5] Data strongly suggests that the fentanyl overdose problem remains unabated. Dissemination of knowledge and promotion of discourse related to this issue will have enormous consequences on long-term public health. This review has two broad objectives. It summarizes the use and abuse of fentanyl via multiple routes of administration and explores emerging frontiers in clinical therapy and treatment methods for fentanyl-related overdoses.

Fentanyl: Historical context and current dynamics

Humans have cultivated *Papaver somniferum* (poppy) for its therapeutic effects for thousands of years. During the early 19th century, alkaloids like codeine and morphine were isolated from opium for the first time. Natural opioids, such as morphine and codeine, are referred to as opiates and were used as starting materials for semi-

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synthetic opioids, such as heroin and oxycodone. In 1937, German scientists discovered that meperidine—a chemical unrelated to opiates—had analgesic effects like morphine. In 1939, synthetic opioids led to the development of methadone, a cornerstone in the treatment of chronic opioid dependency. In 1964, four years following Paul Janssen's discovery of fentanyl in 1960, it was made available to European medical practitioners.[6] In contrast to morphine, which is extracted from opium poppies, fentanyl is made from synthetic precursors that are readily available at a low cost.

Fentanyl pharmacokinetics: Fentanyl is a highly potent, synthetic, Schedule II opioid receptor agonist used to treat chronic pain.[7] It is highly lipophilic and can cross the blood-brain barrier easily, facilitating its relatively quick onset of action within 30-60 minutes. Despite its short half-life of 3-12 hours, fentanyl has been described as the most potent and fastest-acting opioid ever discovered, 50-100 times stronger than morphine.[8,9] Fentanyl has a high first-pass metabolism (about 31% to 65%), resulting in incredibly low oral/buccal bioavailability. Thus, fentanyl is administered intravenously, while it is a lipophilic substance, and its low molecular weight enables its absorption through the skin. Fentanyl was introduced as an intravenous anesthetic under the brand name Sublimaze® in the early 1970s.[6] Despite its effectiveness, fentanyl use in non-perioperative cases is limited due to its parenteral administration. This unnecessarily invasive practice may result in hematoma, infection, nerve damage, and other complications. In the mid-1980s, non-parenteral fentanyl formulations gained clinical and commercial interest. An attractive alternative to oral and parenteral drug delivery was transdermal drug delivery.

Transdermal fentanyl formulations

In 1986, a US patent disclosed a transdermal system designed to deliver free-base fentanyl.[10] Later, in 1989, fentanyl was formulated into a transdermal therapeutic system (TTS-fentanyl, Duragesic®, ALZA Corporation). In patients treated with TTS-fentanyl, morphine usage decreased after 24 hours, and pain scores improved significantly.[11] The TTS-fentanyl patch comprises a rectangular transparent unit enclosed in a protective outer backing layer cover, a fentanyl drug layer with dipropylene glycol and hydroxypropyl cellulose, a rate controlling ethylene, vinyl-acetate copolymer membrane, and a reservoir encased in a protective liner with silicone adhesive.

In 2006, it was reported that fentanyl could leak out of the reservoir, dramatically increasing its potential for overdose. The reservoir patch is also more accessible to drug abusers since it uses fentanyl solution instead of a reservoir.[12] Efforts are being made to overcome the disadvantages of transdermal reservoir systems with newer passive formulations of fentanyl described in a US patent.[13] If there is no liquid reservoir, there is no risk of massive resorption, and therefore no risk of overdosing. In matrix patch systems, drug release is controlled by an inert polymer matrix. This method reduces drug leaks and makes intentional extraction of the active drug from the patch. Fentanyl particles are suspended in solvated silicone adhesives or mixed with silicone fluid. The dissolved adhesive can be mixed with fentanyl suspensions made from silicone fluid and dissolved silicone adhesive.

In 2009, Alza developed a modified matrix patch (Duragesic® D-TRANS® system). It produced a steady-state blood level of fentanyl that lasted 2 to 3 days with a single patch to manage chronic pain. Reaching steady-state concentration produced severe respiratory depression at low doses in opioid-naive patients.

Fentanyl absorption can be enhanced by applying a small electric current to salts like morphine HCl and fentanyl citrate. In addition, the iontophoresis technique has widely been studied for facilitating opioid absorption through the skin.

Iontophoresis: as a transdermal drug delivery method, iontophoresis uses an electric field to propel electrically charged drug components through the skin. The fentanyl ITS (Iontophoretic Transdermal System) effectively treats acute postoperative pain and is well-tolerated by patients.[14] In 2006, an integrated one-piece system, IONSYS, was introduced. This system includes a drug-containing hydrogel sandwiched between two electrodes, with the lower electrode adhered to the skin. An iontophoretic device is usually confined to hospitals and operated by qualified medical personnel. Patients can, however, activate it in emergency pain situations. Several devices became activated during storage because of corrosion caused by drug units with hydrogels and electronic components. In 2007, the device was voluntarily withdrawn from the market because of a high rate of respiratory depression. In 2016, modified fentanyl ITS devices with hydrogel reservoirs attached to skin adhesives were developed. Dosing parameters are fixed, reducing operator error in programming. In postoperative pain management, fentanyl ITS is convenient and easy to use. It is a non-invasive treatment method, unlike intravenous patient-controlled analgesia methods. This device is attached to the upper arm or chest of the patient using the adhesive backing. The main drawbacks of fentanyl ITS are the need for patients to remain in the hospital and the increased respiratory depression caused by fixed-dose formulations. As of 2020, the fentanyl ITS system is discontinued from the market in the USA. Formulations that deliver immediate-release fentanyl transmucosal will overcome the limitations of intravenous fentanyl in treating acute pain.

Transmucosal immediate-release fentanyl formulations (TIRF)

Notably, TIRF provides analgesia comparable to breakthrough cancer pain (BTCP), in large part because

of its pharmacokinetic properties. Moreover, TIFR is easier to use compared to other immediate-release opioids such as morphine and oxycodone. The first transmucosal preparation was introduced in the United States in 1993 as Oralet – a lollipop containing fentanyl citrate - for transmucosal absorption in pediatric anesthesia.[15] In 1998, Actiq®, a modified fentanyl "lollipop," was launched in the USA to treat breakthrough pain in opioid-tolerant patients. It subsequently became successful and revolutionized pain management.[16] The success of these preparations led to the development of a series of transmucosal fentanyl preparations.

In 2006, the US FDA approved Fentora®, an effervescent buccal tablet. In 2009, Onsolis®, a buccal film, received FDA approval. It has fentanyl citrate embedded in a biodegradable polymer, which dissolves between the cheeks and gums.[17]

In 2011, the US FDA approved Abstral® sublingual tablets and Lazanda® intranasal spray to treat breakthrough cancer pain. It disintegrates into small particles, which should not be swallowed whole. Fentanyl is on the outer layer of the sublingual tablet and is absorbed in 30 minutes. It can then be swallowed. Fentanyl is mixed in a phosphate buffered solution for intranasal use. Devices can be a single dose or multiple doses. Lazanda nasal spray has pectin, which forms a gel on the nasal mucosal surface. Later in 2012, Subsys®, a sublingual spray formulation, was approved for the BTCP (breakthrough cancer pain). Onsolis buccal films and Abstral sublingual tablets are discontinued in the US market.[18]

Kinetically, the absorption profile of buccal or sublingual medication differs from oral medications. Fentanyl swallowed orally is excreted through intestinal or hepatic first-pass metabolism. Vasoconstriction can affect nasal mucosal perfusion, which controls the amount of air taken in through the nose. TIRF medications cannot be interchanged regardless of the route of administration, as absorption of fentanyl varies because of different pharmacokinetics. TIRF should not be prescribed to patients who do not tolerate opioids because they have an acute onset and high potency. In patients who cannot tolerate opioids, a single dose of TIRF may cause an overdose. Patients who take 60 mg of oral morphine per day are the only ones who can receive transmucosal fentanyl. Overall, the novel fentanyl formulations have allowed fentanyl to be used in non-perioperative conditions. They have changed pain management for cancer patients, prehospital and critically ill patients, pediatric patients, and postoperative patients. In recent years, the use of TIRF has increased. Compared to oral morphine and oxycodone, rapid-acting fentanyl significantly improves pain intensity by 50%.[19]

TIRF is used to treat acute pain in the hospital setting, or if a patient needs it at home, they must be enrolled in a program approved by the FDA.[20] The Risk Evaluation and Mitigation Strategy (REMS) Program for TIRF is an FDA-mandated program that ensures informed risk-benefit decisions before and during treatment. The goal of the REMS is to prevent people from misusing, abusing, becoming addicted to, overdosing on, or getting other serious health problems from taking TIRF medicines.

TIRF medications should be prescribed according to REMS guidelines. It is highly recommended that treatment begins at the lowest possible dose. Oral mucosal fentanyl should always be re-titrated at the suggested starting dose if either the usual background opioid dose is raised, or the brand being used is changed.

According to REMS assessment reports, in 2018, many patients prescribed TIRF medicines may not have been opioid tolerant when they received a new prescription for a TIRF medication. TIRF medicines can cause breathing problems in opioid-naive patients. Prescription of these products should consider their abuse potential. Prescribing physicians have consistently violated the FDA Risk Mitigation Strategies.[20,21] In a recent study, 11.6% of prescribers claimed that rapid-acting fentanyl could be used with patients who had never previously used opioids. The REMS program outlines dis-enrollment measures. However, they have not been used. In a retrospective study, in 11% of patients with breakthrough pain, aberrant behavior was found relative to the use of transmucosal fentanyl.[22,23] A study performed in France from 2010 to 2015 found that 84% of patients were using TIRF. However, it did not represent the entire population and only considered cancer and non-cancer treatments.[24] According to a study conducted in France, off-label prescribing of TIRF is extremely common, so it is imperative to understand the need for TIRF authorization of prescription and clinical use to decide whether such use carries a favorable benefit/risk ratio.[25] Table 1 summarizes the different fentanyl formulation available and their characteristics.

Misuse of prescription fentanyl

Defining drug "use" and "misuse" using qualitative on quantitative terms is challenging. Misuse and "non-medical usage" represent a wide range of actions and motives that do not include higher doses, frequent dosing, prolonged therapy duration, alternate modes of administration, and co-administration with any other drug. Misuse of a therapeutic drug can be intentional or unintentional; for example, when a physician prescribes transdermal treatment to treat acute pain, a physician recommends cutting the patch to reduce the dose, or a patient applies multiple prescriptions for analgesia, which the physician inadequately informs. The term "abuse" refers to intentionally using a drug or its contents in ways that were not intended or recommended. The motives behind drug abuse are vast, ranging from recreation to self-harm.

In 1972, as fentanyl became more popular and widely available as an adjunct to surgery, early reports emerged

Table 1. Different fentanyl formulations and their characteristics

Dosage Form	Approval date	Manufacturer	Brand name	Onset Time	Bioavailability	Duration of Action	Mkt. Status
Troche/Lozenge	Nov 4, 1998	Cephalon	Actiq®	4.2 min (for 200 µg, 800 µg)	50%	145 min for 200 µg	Rx [6]
Buccal tablet	Sep 25, 2006	Cephalon	Fentora®	10 min	65%	60 min	Only 300 mg tablets were Disc on Mar 2, 2007 [26]
Buccal film	Jul 16, 2009	BioDelivery Sciences International, Inc.	Onsolis®	15 min	71%	60 min	Discontinued [27]
Sublingual tablet	Jan 7, 2011	Sentynl Therapeutics	Abstral®	4.2 min	70%	60 min for 100-800 µg	Discontinued [28]
Sublingual spray	Jan 4, 2012	BTCP Pharma	Subsys®	5 min	76%	60 min	Rx [29]
Nasal spray	2009, in France	Takeda	Instanyl®	2-5 min	89%	120 min for 75 µg	Rx [30]
	Jun 30, 2011	BTCP Pharma	Lazanda®	10 min	120%, relative to Actiq®	60 min	Discontinued in 2015 [31]
Transdermal patch	August 1990	Janssen Pharmaceuticals	Duragesic®	12-24 hrs.	92%	Up to 12 h after the patch removal	Discontinued in 2020 [32]
Iontophoresis	Sep 25, 2006	The Medicines Company	Ionsys®	15 min	41% in 1 h and 100% in 10 h	45 min per dose Of 40 mg	Discontinued in 2007 [33]

of intentional misuse of fentanyl among anesthesiologists and surgeons.[34-36] The first report on fentanyl abuse involved six health care professionals, including three anesthesiologists and three nurse practitioners.[36] In 1970, 1.3% of anesthesiology trainees misused fentanyl.[37,38] Fentanyl abuse increased among anesthesiologists and health care staff because of accessibility at work.[35,39-41] To treat chronic pain, novel delivery systems were developed to deliver fentanyl analogs during the 1980s. For example, carfentanil, used in veterinary medicine, is a fentanyl analog that has a 100 times greater affinity for µ receptor than fentanyl.[42,43] There were no apparent signs of abuse of fentanyl products outside of medical settings. In 1994, the FDA issued a precautionary warning to physicians not to prescribe fentanyl to opioid-naive patients,[44] and a supplemental warning in 2005 and 2007. Fentanyl and sufentanil, a fentanyl analog, are the most abused drugs among anesthesiologists.[45-47]

Fentanyl sales in the United States increased tenfold within a year after it went off-patent. In addition, using fentanyl transdermal patches was extended from clinicians to patients for widespread palliative care. Fentanyl used for recreational purposes is derived from clandestine sources and Fentanyl Transdermal patches. Fentanyl Transdermal patches abused by tampering can cause an increase in the dose administered.[48]

Patches having fentanyl reservoirs are abused in many ways. The drug reservoir layer allows fentanyl to be extracted and injected intravenously, causing fatal overdoses. The most typical manifestations of an overdose are coma, lethargy, respiratory depression, and cardiac arrest, leading to death. In 1993, DeSio et al reported a case of abuse where a patient aspirated the gel reservoir patch and injected it into her indwelling central venous catheter.[49] Reeves and Ginifer reported seven cases of intravenous misuse.[50] Inhalation abuse by heating transdermal fentanyl was reported.[51] Other reported methods of abuse include eluting fentanyl from the patch in hot water like a tea bag[52] and inserting a transdermal patch rectally.[53] Kramer and Tawney (1998) reported an overdose of transdermal fentanyl via mucous membrane absorption.[54] Accidental misuse of fentanyl occurred in a transdermal system overdose because of a heating pad.[55] As of 2006, there were 16,012 emergency department visits because of the recreational use of fentanyl.

In 2009, a matrix transdermal patch was developed to overcome the drawbacks associated with the fentanyl reservoir patch, which reduced drug leakage and misuse by extraction.[56] In contrast, Canadian opioid addicts preferred the matrix transdermal device as it offered rapid transmucosal absorption by cutting to the desired size.[57] All the case reports of abuse are summarized in Table 2.[32,58-61]

Despite its low oral bioavailability, ingesting fentanyl patches can cause poisoning and death.[62-67] Whether transdermal device ingestion causes fatalities is not clear to what extent the absorption of these devices occurs under the tongue, through the mucosa, or the gastrointestinal tract, or if they happen in combination. Abuse, overdose, and even death can when patches are used sublingually[68] through ingestion[69] or by intravenous administration of fentanyl extracted by boiling.[70] Even after use, the residual amount of drug in the patch is 28-84 percent of the first drug, which can be lethal, so proper disposal policies are needed.[71] An abuser used Transdermal fentanyl devices from deceased and nursing home patients in 1996,

Table 2. Case reports of prescription fentanyl abuse

Number of case reports	Gender, age	Route of abuse	Cause of death	Ref.
Case report (N=6)	NR	Intravenous	Intentional abuse Health care professional	36
Case report (N=1)	33 M	Intravenous	Intentional abuse Health care professional	34
Case report (N=1)	31 M	Intravenous	Intentional abuse Health care professional	35
Case report (N=1)	23 M	Intravenous	Intentional abuse Health care professional	40
Case report (N=1)	36 M	Intravenous	Intentional abuse Health care professional	75
Case report (N=1)	35 M	Intravenous	Intentional abuse Health care professional	39
Case report (N=1)	21 M	Intravenous	Intentional abuse via an indwelling central venous catheter	49
Case report (N=30)	26 M, 4 F	Intravenous	Intentional abuse	76
Case report (N=1)	NR	Intravenous	Intentional abuse	72
Case report (N=9)	M (22-44)	Intravenous	Intentional abuse	77
Case report (N=1)	36 M	Inhalation	Intentional abuse heated the patch	51
Case report (N=1)	83 F	Transdermal	Undetermined	59
Case report (N=1)	31 M	Transdermal	Accidental (patches from a deceased person in a nursing home)	78
Case report (N=1)	31 M	Transdermal and oral	Accidental	54
Retrospective study (N=25) 7 F, 18 M	F: 19 to 86 M: 18 35	24 Transdermal; 1 transdermal + Intravenous	5naturals, 3 suicide, 15 accidental and 2 undeterminated	79
Case report (N=1)	57 F	Transdermal	Accidental misuse in the operation of theater heating blanket increased the percutaneous absorption of fentanyl	60
Case report (N=1)	34 F	Intravenous	Accidental Overdose	80
Retrospective study (N = 23)	NR M	3 Oral 5 transdermal; 2 transdermal; 4 intravenous; 9 NR	2 Natural,1suicide,20 accidental overdose	67
Case series (N=2)	M from 35 to 42	Intravenous	Accidental overdose	58
Case series (N=4)	38 M, 42 F, 39 M, 35 M	Intravenous	3 Accidents and 1 suicide	32
Case report (N=1)	21 F	Oral	Intentional abuse -Boiling up fentanyl patch in tea bag	52
Case report (N=1)	41 M	Rectal	Intentional abuse	53
Retrospective study (N=112) 63 M, 49 F	4-93	Transdermal, intravenous; oral; inhalation	11 natural,6 suicide,57 accidental, and 38 Undetermined	81
Case report (N=1)	F 1	Oral	Accidental overdose.	63
Case report (N=1)	78 F	10, 100 mg Fentanyl transdermal patches	Intentional abuse to suicide death	82
Retrospective study (N=23)	NR	7 transdermal; 16 NR	1 Natural and 6 accidental deaths.	83
Case report (N=1)	M 42	Transdermal and oral	Accidental overdose	84
Case report (N=1)	M 63	Transdermal	Suicide	85
Case report (N=7) 3F, 4M	20-51	6 oral 1 transdermal	Accidental overdose	61
Case report (N=1)	M 32	Transdermal	Accidental overdose	86
Case report (N=1)	M 28	Oral	Accidental overdose	87
Case series (N=8) 3F, 5M	16-49	Transdermal	Accidental overdose	88
Case report (N=1)	42F	11 Transdermal fentanyl patches each of 100 µg/h (dose)	Intentional abuse to suicide	89

Table 2. Continued

Number of case reports	Gender, age	Route of abuse	Cause of death	Ref.
Retrospective study (n =92), 40 F, 52 M	13-86	Transdermal	36 Natural, 8 suicides, 5 dosing errors, 40 accidental 3 undetermined	90
Case report (N=1)	46 F	34 matrix-based fentanyl transdermal patches	An assisted suicide	91
Case report (N=10)	NR	Transdermal	Accidental or suicidal	92
Case report (N=3)	76 F, 47 M, 52 M	Transdermal	Intentional abuse to treat pain	93
Case report (N=1)	2 F	Transdermal	Accidental overdose	94
Case report (N=1)	2 M	Transdermal	Accidental overdose	74
Case report (N=1)	42 M	Transdermal and oral	Accidental overdose	68
Case report (N=1)	54 F	Oral	Suicide	95
Case report (N=57), 51 M, 6 F	19-63	Transdermal and illicit fentanyl	Intentional abuse	96
Retrospective study (N=242), 198 M, 44 F	18-62	1 inhalation; 10 oral + Intravenous; 2 oral, 12 transdermal + Intravenous; 4 transdermal; 72 Intravenous; 141 NR	Matrix patch death	97
Case report (N=1)	70 F	Transdermal	Intentional abuse to suicide But woke up in the emergency after a long sleep	98
Retrospective study (N=35), 20 F, 15 M	17-95	Transdermal	21 Natural, 9 accidental, 5 undetermined	99
Case report (N=1)	F 40	Transdermal	Accidental overdose	100
Retrospective study (N=8663)	NR	Oral, Transdermal	85 deaths were related to fentanyl patch	101

F, Female; M, Male; NR, Not Reported; IV, Intravenous.

prompting hospitals to develop disposal policies.[72] FDA and manufacturers educate patients to flush transdermal devices down the toilet to prevent unintentional exposure to children.[63,73,74] According to the Centers for Disease Control and Prevention, the national opioid dispensing rate in 2020 was 43.3 prescriptions per 100 people, the lowest level in 15 years (i.e., more than 142 million opioid prescriptions) since 2006, when the total number of prescriptions was more than 255 million.

Misuse of illicitly manufactured fentanyl (IMF)

Illicit fentanyl – which refers to fentanyl and fentanyl analogues manufactured outside of the scope of regulated medical practice – is responsible for an increased rate of opioid overdose despite an overall decrease in prescription rates. Their variation in potency of a few fentanyl analogs compared to fentanyl is listed in Table 3.

Illicit fentanyl & Fentanyl analogs are becoming increasingly popular due to their addictive properties. The potency of fentanyl analogs can expose first responders and users to unintentional overdoses.[103] In addition to their potency, lethality, and variability in supply, illicitly manufactured fentanyl carries a substantial risk of overdose, mainly when used by opioid-naive individuals or those whose tolerance has decreased because of withdrawal symptoms.[104] As heroin availability, purity, and prices have decreased in Europe and the US, illicit fentanyl use has skyrocketed. Since 2013, illicitly manufactured fentanyl and fentanyl analogs have become ubiquitous, leading to the global opioid crisis, particularly when combined with heroin and other drugs.[2,105]

Illicit fentanyl has many street names "Designer drug," "China White," "Apache," "Flatline," "Lethal Injection, "Chinatown," "Great Bear," "Dance Fever," and "Poison." Between 1979 and 1988, in Orange County, California, the first large-scale illicit fentanyl abuse was reported where alpha-methyl fentanyl (AMF), a fentanyl analog, was sold as heroin.[106-109] Several other analogs were found on

Table 3. Estimated relative potency of fentanyl analogs102

Fentanyl analogs name	Estimated relative potency compared to fentanyl
Remifentanil	1
Sufentanil	10
Alfentanil	0.3
Carfentanil	30-100
Acetyl fentanyl	0.3
Alpha-methyl fentanyl	1
3-Methyl-fentanyl	0.9-10.5
Butyryl-fentanyl	0.03-0.13
Ocfentanil	2.5
Cyclopropyl fentanyl	3
Furanyl-fentanyl	7
4-Fluoro-fentanyl	0.29

the black market in the late 1980s that caused overdose deaths.[109] In Pennsylvania, 3-methyl fentanyl caused 14 overdose deaths in 1984.[110] In 1995, Sweden reported its first fatal 3-methylfentanyl case.[111] Later in 1995, in Estonia, 3-methylfentanyl was marketed as a substitute for heroin, caused of over 1,100 deaths between 2005 and 2013.[112]

In 2006, there was an outbreak of fatalities among illicit drug users due to the adulteration of cocaine with fentanyl. Since many cocaine users may be opioid-naïve, there is a significant clinical risk. Several cases of accidental fentanyl intoxication have been reported after the consumption of cocaine.[113] From Apr 4, 2005, to Mar 28, 2007, 1013 illicit Fentanyl heroin or cocaine-laced fentanyl-related deaths were reported from six states, so the DEA (Drug Enforcement Administration) identified Toluca, Mexico, as the origin of deadly fentanyl. The outbreak ended in 2007 when the DEA scheduled the fentanyl precursors and seized the laboratory.[114]

Between 2012 and 2014, there was an alarming rise in fake prescription pills laced with illegal fentanyl analogs. In 2013, acetyl-fentanyl, a black-market fentanyl analog, caused overdose deaths in the USA, Japan, Australia, and Sweden.[115-123]

In 2014, the first case of butyryl fentanyl, a fentanyl analog, was documented in Kansas. Since then, other cases have been recorded in Illinois, Minnesota, and Pennsylvania. According to the DEA, 40 overdoses are confirmed to be due to butyryl-fentanyl by the end of 2015 (DEA, 2016a). Standard immunoassays cannot differentiate butyryl fentanyl and beta hydroxythiofentanyl from fentanyl, so they are under-reported. An accidental overdose case of Butyryl-Fentanyl was also reported.[124] In 2015, seven confirmed overdoses of the novel fentanyl analog beta-hydroxythiofentanyl were reported in Florida and Oregon. According to DEA2016a, most of the opioid overdose deaths in 2016 were caused by fentanyl and its analogs, like acetyl fentanyl, furanyl fentanyl, and carfentanil. All the clusters of cases that documented illicit fentanyl deaths are summarized in Table 4.

Montgomery County, Ohio, had twice as many illegal fentanyl analog deaths in 2017 compared to 2015. A significant outbreak of fentanyl-contaminated pills occurred in California. In 2016, 8 people died from fentanyl-laced alprazolam, while 18 patients were admitted to hospitals from fentanyl-laced hydrocodone/acetaminophen overdose.[150] A bizarre case of fentanyl, methamphetamine, and amphetamine administration in

Table 4. The cluster of cases that documents illicit fentanyl death

Duration and location	Overdose deaths	Cause of death	Ref.
1979-1988, California (USA)	N=112	IMF and Alpha-methyl fentanyl are sold as a heroin alternative, IV abuse	108, 109
1984, Pennsylvania (USA)	N=14	3-methyl fentanyl, IV abuse	110
1992, Maryland (USA)	N=30	IMF with ethanol	76
1997-2005, Minneapolis (USA)	N=19	IMF accounted for 8eightdeaths, and IMF and other drugs caused 11 deaths	83
Apr 1, 2005–Dec 31, 2006, IL (USA)	N=342	IMF, cocaine, and ethanol	125
Dec 10, 2006, Michigan (USA)	N=178	Heroin mixed with IMF	
Camden, New Jersey (USA)	N=42	IMF	
Sep 2005–Nove2006, Massachusetts (USA)	N=107 (74 M; 33 F)	55 of IMF and Co administered cocaine, 26 indeterminate cases,26 licit use	126
October–November 2002, Finland	N=3 (2 M; 1 F)	3-Methyl fentanyl Intravenous abuse	127
2005–2006, Estonia	N=117 (107 M, 10 F)	3-Methyl fentanyl Intravenous abuse	112
July 2005–May 2006, Michigan, Wayne County (USA)	N=101 (61M,40F)	IMF, heroin-associated fatalities	114
Oct2014–March 2015, Massachusetts (USA)	N=125 (100 M,25 F)	IMF, cocaine, heroin-associated fatalities	128
2015, Kentucky (USA)	N=308	IMF, heroin-associated fatalities	129
Oct 2013-April 2014, Montgomery county, FL (USA)	N=810	Illicit fentanyl with cocaine and other drugs	130
Florida (USA) , 2014	2010–2012 (N=379) 2013-2014 (N=582) Jan-June 2015 (N=289)	Illicit fentanyl with cocaine, heroin, and other drugs	131
July 2014-Jan 2015, Florida (USA)	(N=72) 51M,21F	Illicit fentanyl with cocaine, other drugs	96
2014, Ohio (USA)	N=456 319 M,137 F	IMF, cocaine, heroin-associated fatalities	

Table 4. Continued

Duration and location	Overdose deaths	Cause of death	Ref.
2014-2015, Tampa, Florida (USA)	N=7 Age: 46,39, 41,55, 28,30, M, 26, F	Acetyl fentanyl, heroin, or other opiates/opioids were present in all cases.	132
2015-2016, California (USA)	N=8	Street-purchased counterfeit Xanax and Norco pills	133
In June 2016, Connecticut	N=13	IMF contaminated cocaine	99
October 2016 and April 2017, Pennsylvania (USA)	N=355	Carfentanil	134
2002, Moscow	N=125	Carfentanil to subdue terrorist	135
2017, Hillsborough county, FL	N=2 Age: 34 M; 25 M	Accidental toxicity Carfentanil	136
2012, England	N=25	Carfentanil combined with fentanyl and morphine	137
March-May 2013, Rhode Island (USA)	N = 14 (10 M, 4 F) Age 19-59	Acetyl fentanyl	115
January 2015-February 2016, Pennsylvania (USA)	N=41 (10 F; 31 M)	26 Cases involved fentanyl; one case involved multiple substances &Acetyl fentanyl	122
November 2014, California (USA)	N=1 Age: 24, M	Accidental acetyl fentanyl Intoxication, previous history of heroin abuse.	116
2016, Japan	N=1 Age: 32, M	Acetyl fentanyl Intoxication	138
2016, Japan	N=1 Age: 32, M	Acetyl fentanyl Intoxication	139
2015-2016, Florida (USA)	N=1 Age: 28, M	Acetyl fentanyl + fentanyl	121
2014, West Virginia (USA)	N=1 Age: 28, M	Acetyl fentanyl	118
2014, Texas (USA)	N=1 36, M	Acetyl fentanyl sols as an E-cigarette patient survived in the emergency department	119
2016, Oklahoma (USA)	N=2 Age: 20 M, 59 F	20 M, History of abuse 59 F, prescription drug abuse	120
November 2015, Sweden	N=14	Acetyl fentanyl, 4-methoxybutyrfentanyl and furanyl fentanyl intoxications Nasal and oral abuse	140
2015, Australia	N=1 Age: 24, M	Acetyl fentanyl Intoxications	141
2014, Minnesota	N=1 Age: 18, M	Butyryl fentanyl	142
May 2015, California (USA)	N=1 Age: 44, M	Butyryl fentanyl and Acetyl fentanyl History of heroin use.	143
2015, Florida (USA)	N=2 Age: 53, 49, F	Butyryl fentanyl 49 F Acetyl fentanyl has been detected to have a history of anxiety, bipolar disorder, and two previous suicide attempts 53, F, History of smoking, prescription drug abuse, and psychiatric disorder hospitalization.	124
2016, Switzerland	N=1 Age: 23, M	Butyryl fentanyl Nasal route	144
2015-2016, Florida (USA)	N=7	Beta-hydroxythiofentanyl	121
2015–2016 Sweden	N=7 Age:26-36 M	Furanyl fentanyl	145
2016, Poland	N=2 Age:26, M25 F	4-Fluorobutyrfentanyl	146
2016, Belgium	N=1 Age: 17 M	Ocfentanil history of illicit drug abuse and depression	147
2016, Switzerland	N=1 Age: 24 M	Ocfentanil	148
July 2016, Ohio (USA)	N=5 2 M, 3 F	Acetyl Fentanyl, furanyl fentanyl 3-methylfentanyl, and carfentanil	149

F, Female; M, Male; NR, Not Reported; IV, Intravenous.

human blood was reported.[151]

In 1990, ocfentanil was developed for medical use as an analgesic with fewer cardiovascular and respiratory adverse effects than morphine was used as heroin adulterant. A case of the first ocfentanil overdose-caused death was reported in a 17-year-old with a history of drug misuse who snorted a brown powder bought online with bitcoins.[147] During the siege of the Melnikov Street Theatre in Moscow in 2002, an aerosol containing carfentanil was used to incapacitate the terrorists. This opioid is used primarily as an incapacitating agent for large animals; there has also been a report of recreational use of carfentanil.[152,153] A 26-year-old male and a 25-year-old female were found dead at home after ingesting 4-fluorobutyrfentanyl.[146] A case of polysubstance abuse was reported where furanyl fentanyl and 2-methyl-4- (methylthio)-2-morpho'inopropiophenone (MMMP) were found in the deceased's postmortem.[154] A fatal overdose of furanyl fentanyl and 4-anilino-N-phenethylpiperidine (4-ANPP) was reported in a 23-year-old male in San Francisco after taking fake oxycodone.[155] With smartphones, drug user buy fake pills online, harming their health. A Case report describes a 27-year-old man who smoked and snorted four online-bought "M30" blue pills, causing severe kidney failure requiring hemodialysis.[156]

Pediatric misuse of fentanyl is described as two cases via "M30" pills reported in a study.[157] A Case Series described 4 cases of the children in this study with a history of parental substance abuse disorder.[158] Another case report shows the need for systematic toxicological analysis regardless of the situation, age, or drug user. In postmortem reports for three children, two showed fentanyl in their systems, and one showed fentanyl and opiates in their systems.[159] Recent rises in drug overdose and mortality together with the emergence of strong synthetic opioids like carfentanil have increased worries about work-related exposure to illicit narcotics among law enforcement personnel, emergency responders, and other US workers.[160] Besides having a high potency, fentanyl analogs are toxic when accidentally exposed, according to a study done in Sweden on patients suspected of being exposed to a new psychoactive substance. Three of four patients' serum or urine samples had butyl-fentanyl, 4F-butyr fentanyl, and fentanyl.[161] In 2017, two Cyclopropyl fentanyl accidental overdoses were reported in the United States and one in Spain.[162] The opioids, U-47700, AH-7921, U-50488, and U-77891, structurally unrelated to fentanyl, have emerged as a significant public health concern, contributing to overdoses. Many reports have been published about fatal overdoses from abuse of U-47700.[163]

Clinical manifestation

The prevalence of fentanyl use is almost 40% among those entering opioid addiction treatment programs. Many people are unintentionally exposed to fentanyl, yet it has become their preferred opioid. Fentanyl misusers underestimate its potency and risk death because of its euphoria. Besides of its potent analgesic and euphoric properties, fentanyl causes sleepiness and relaxation like other opioid agonists.[164] Clinical effects result from severe central nervous system depression, leading to loss of protective reflexes and respiratory depression.[165] A single intravenous dose can cause respiratory depression lasting up to 23 hours.[166]

There have been several overdose symptoms associated with fentanyl and its analogs. A study of fatal opioid overdoses between 2012 and 2014 identified rare signs, including blue lips (20%), gurgling sounds (16%), rigidity or bewilderment (6%), and perplexity before unresponsiveness (6%).[128] Using fentanyl can lead to rare adverse effects, including diffuse alveolar hemorrhage in patients with hypoxic respiratory failure[167] and rapid death because of chest wall rigidity.[168, 169] Foy et al. described a pediatric case of a 19-month-old girl who was unresponsive after inadvertently placing a fentanyl transdermal patch on her back—demonstrated toxic leukoencephalopathy on Magnetic Resonance Imaging, characterized by changes in cerebellar white matter. In another case, a woman with knee pain took three fentanyl patches and went to the emergency room with fainting and chest pain that looked like acute coronary syndrome.[170] Despite such findings, data available at these levels do not provide much insight into poisoning management because patient demographics, dosage, and treatment methods vary widely.

Treatment/Management

Naloxone

Acute intoxication with fentanyl leads to respiratory failure that appears in a few minutes and requires immediate care by ventilatory support and oxygenation. If oxygenation fails and the respiratory rate drops below ten breaths per minute, naloxone binds to opiate receptors and acts as a competitive antagonist. It is administered intravenously, intramuscularly, subcutaneously, or via an endotracheal tube.

A new nasal formulation approved by the FDA could help treat people who do not have access to IV. The starting dose of naloxone for adults is 0.4 to 1 mg, and for children, it is 0.1 mg/kg with an onset of action of 3-8 minutes. If breathing is shallow, a bag-valve ventilation system or 100% FI02 is recommended until the patient is awake and cooperative. Chronic opiate abusers receive 0.1 - 0.4 mg intravenous Naloxone every 1 to 3 minutes to reverse opiate effects and relieve pain. The administration of naloxone intranasally or intramuscularly (2 mg) is a choice for certain overdose patients and long-term drug addicts. Nausea, vomiting, agitation, pain, and aspiration are withdrawal symptoms. Naloxone's half-life is 30 to 45 minutes, and its action lasts 90 to 180 minutes. In rare cases, treating opiate toxicity with a repeat dose is possible. High doses of naloxone are often needed in overdoses

involving diphenoxylate, methadone, butorphanol, and nalbuphine. In addition, new opiate antidotes, such as nalmefene and naltrexone, are on the market. The US FDA approved naloxone in 1971. To reduce opioid-related deaths worldwide, the WHO (World Health Organization) published dosing guidelines on November 4, 2014. Different nasal sprays of naloxone can help in emergencies. Although Naloxone is the standard treatment for fentanyl overdose, attempts to revive patients could prove unsuccessful due to the rapid acting nature of fentanyl. The prevalence of this fentanyl abuse therefore calls for innovative and effective technologies and strategies to curb the menace.[171] Inhaling fentanyl base is a rare abuse method. The 36-year-old male abused fentanyl patches by inhalation. He responded well to naloxone injections, which quickly brought him back to consciousness.[51] Fentanyl is abused in various forms. Barreto et al. analyzed a case where a patient was resuscitated with naloxone iv after drinking a mixture of fentanyl patches and hot water.[52] Naloxone may be best avoided for mildly poisoned patients with non-vomiting and opioid-tolerant with adequate spontaneous ventilation. Bag-valve-mask ventilation is the most used method to supply ventilation for patients. However, endotracheal intubation or other measures like extracorporeal membrane oxygenation may also be needed.[172] Shigematsu-Locatelli, Kawano, et al. found that sustained-release tramadol could detoxify patients during long-term non-cancer therapy induced by fentanyl iatrogenic opioid dependence.[173] In 2010, Prosser et al studied fentanyl abuse cases reported by the New York Poison Control Center from January 2000 through April 2008. The findings showed that 38% of the patients treated with Naloxone had a positive outcome.[174] D'Orazio et al analyzed a series of four patients who ingested the gel reservoir of a fentanyl transdermal patch and responded well to the first prehospital doses (0.8-2 mg intravenously) of Naloxone but later developed recurrent respiratory depression.[175] Thornton et al. analyzed the transdermal drug delivery exposures reported to the National Poison Data System (NPDS). Naloxone was given in 1080 cases of 6746 adults and 1917 pediatric exposures due to fentanyl poisoning.[176] Although Naloxone antagonizes the opioid effects of fentanyl may avoid intubation for some patients; Naloxone may be best avoided for mildly poisoned, non-vomiting, and opioid-tolerant patients with adequate spontaneous ventilation. Mostly bag-valve-mask ventilation is the method used to supply ventilation for patients. However, endotracheal intubation or other measures like extracorporeal membrane oxygenation[172] may also be needed.[172] American poison centers reported that 76 patients who consumed whole fentanyl patches had long-term toxicity, with 14 patients requiring intubation and eight receiving naloxone.[69] An analysis found that take-home naloxone programs significantly decreased overdose mortality among participants and the public with little adverse consequences. One in 123 overdoses results in death, according to the WHO.[177] A study conducted in Canada found that fentanyl overdoses and infections increased by 108% during COVID-19. Fentanyl intravenously can impair microcirculation response to brainstem and lung hemorrhage, disrupt respiratory systems, and cause respiratory depression. So, COVID-19 Fentanyl users should be closely monitored.[178,179]

Pharmacotherapies

Some researchers have studied pharmacotherapies' potential in reducing fentanyl addiction and its side effects. However, treating opioid use disorder seems to still require novel approaches and medications. Besides producing antibodies against opioid drugs, anti-fentanyl vaccines also block the penetration of opioids into the brain. Several fentanyl and heroin vaccines have been studied in rodents and nonhuman primates, but they are still in preclinical phases and need to be implemented to clinical use of fentanyl overdose.[180]

Deterrence and patient education

Legislation has been passed in many states to address the opioid epidemic in numerous ways. Drug overprescribing was curtailed by establishing prescription drug monitoring programs (PDMPs).[181] Abuse-deterrent opioid products may reduce overdose fatalities, abuse, and overdose deaths. For example, in comparison with the original oxycodone and abuse-deterrent formulations, reformulated OxyContin showed lower abuse rates,[182] indicating opioid use disorders (27% reduction), overdoses (34% reduction), and fatalities (85% reduction). Therefore, fentanyl is an abuse-deterrent formulation that may reduce the amount of pharmaceutical fentanyl. The safety of opioid formulations should be improved via multiple approaches, and their abuse-related adverse effects should be assessed post-marketing and in real-world settings.

Conclusion

Fentanyl is a highly potent substance and has played a significant role in clinical anesthesia for decades. Inadvertent overuse, purposeful misuse, and epidemics of fentanyl and IMF overdoses have been reported. The easy availability of IMF, fentanyl analogs, and online ordering have contributed to an increase in overdoses as abusers seek out fentanyl-laced items. In addition to closing clandestine labs, limiting precursor materials may be an actionable public health priority. Since IMFs are cheap and easy to hide, it is unlikely that law enforcement alone will be able to stop their spread. Due to their very high potency, fentanyl, fentanyl analogs, and IMF can cause rapid death in patients. Education about overdose prevention and harm reduction is crucial to mitigate fatality rates in the community. The Naloxone rescue kit should be prescribed to every high-risk patient and be available at pharmacies on standing order. Hospitals, clinics, and emergency departments need to establish parameters to

Research Highlights

What is the current knowledge?

√ Current opioid overdose treatments include buprenorphine and naltrexone.

What is new here?

√ We discuss how opioid vaccines and tamper-proof formulations could make them more effective by preventing overdoses.

screen for fentanyl misuse. As a gold standard procedure, treatment medications (i.e., buprenorphine, methadone, and naltrexone) need to be available to all hospitals and clinics. Healthcare providers are constantly challenged to balance medical opioid use with legitimate concerns about abuse, misuse, and diversion. Patient education, vaccine development, and abuse-deterrent formulations are all valuable frontiers in the fight against opioid addiction.

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