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Review Article

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Fentanyl Abuse: A Literature Review

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Abstract

Background and Objectives: *Fentanyl is an opioid agonist with abuse potential. The overdose can begin suddenly, progress to death rapidly, and may have an atypical presentation with body and chest wall rigidity. This article aims to review the consequences of fentanyl abuse alone or in combination with other substances along with available treatment modalities.*

Methods: *A literature search using the keywords "opioid addiction" or "fentanyl abuse" and "fentanyl overdose" and "fentanyl treatment" was conducted on PubMed. Additional data was gathered from the Centers for Disease Control and Prevention and other websites. Finally, 32 out of 310 articles were selected for the review. Our case report highlights the consequences of fentanyl abuse in combination with other substances.*

Case report: *A 32 years old Caucasian female with a history of polysubstance use was admitted for community-acquired pneumonia after overdosing with fentanyl, heroin, and cocaine.*

Results: *Fentanyl is often mixed with other substances and sold as heroin to unsuspecting users. Its abuse may cause life-threatening respiratory failure from an overdose.*

Discussion and Conclusions: *In 2016, approximately 50% who died from an opioid overdose in the US were taking fentanyl, and 57% of those who tested positive for fentanyl or its analogs were positive for other drugs such as heroin. Naloxone kits distribution has reported significant overdose reversals.*

Scientific Significance: *Opioid crisis, declared as an emergency by the federal government, is affecting public health. Prescribers have a major role in reducing overdose deaths by prescribing the lowest, effective dose with the shortest treatment duration.*

Background and Objectives

Fentanyl, a phenylpiperidine synthetic opiate agonist, has abuse potential and risk of life-threatening respiratory failure from an overdose [1]. It was first synthesized from N-benzyl-4-piperidone by Janssen Pharmaceutical in 1960 and was used as an intravenous surgical anesthetic [2, 3]. Introduction of this new drug was important for anesthetic use because of issues with morphine such as incomplete amnesia [4].

Countries like China and Mexico, among others, frequently make the drug and export it illegally to the US [5, 6]. There is an exponential increase in illicit fentanyl use mainly in North America, leading to serious intoxications [7]. In 2017, 70,200 Americans died of drug over dosages; out of those about 28,400 deaths were caused by fentanyl and its analogs [8]. Drug dealers purchase fentanyl or its analogs at low cost (wholesale cost for fentanyl is about twenty times cheaper than heroin) and often use it as an adulterant to heroin which has resulted in a marked increase in overdose deaths in recent years [3]. In 2016, at least 50% who died from an opioid overdose in the US were taking fentanyl, and 57% of those who tested positive for fentanyl or its analogs were also positive for other drugs such as heroin. A new trend is mixing fentanyl with cocaine to combine the effect of a CNS depressant with a stimulant, thus helping to counteract the after-effects. Fentanyl is also combined with substances such as alcohol, benzodiazepines, antidepressants, antihistamines, antipsychotics, psych stimulants like amphetamines, and other opioids or anesthetics [9]. To make it worse fentanyl is being sold as counterfeit pain and anxiolytic medications. The risk of fatal overdose is significantly higher because users of these substances are not only unaware of it but also might not have a tolerance to opioids [10]. A lethal dose of fentanyl is lower than that of heroin, and fentanyl analogs such as carfentanil have an even smaller lethal dose (Figure 1).

Figure 1: A lethal dose of fentanyl compared to heroin and carfentanil (Carfentanil is an analog of fentanyl; a lot more potent than fentanyl). Picture obtained with permission from Bruce A. Taylor, NH State Police Forensic Lab [11].

Fentanyl is 50 times more potent than heroin and 100 times more potent than morphine [12]. It is highly lipophilic; rapidly crosses the blood-brain barrier accounting for its fast onset of action (2-5 min). Additionally, its level quickly declines due to rapid sequestration into body fat, contributing to its shorter duration of action. Moreover, its high potency with the above properties significantly increases the risk of addiction, overdose, and withdrawal [10]. Slow release of fentanyl into the blood from fatty tissues may lead to a rebound in serum fentanyl concentrations accounting for delayed effects of fentanyl even after its discontinuation [13].

Common side effects of fentanyl include dizziness, drowsiness, nausea, vomiting, headache, and constipation, and euphoria. Overdose symptoms consist of miosis, respiratory depression, bradycardia, and hypotension. Without prompt treatment with naloxone, respiratory depression may ensue, resulting in respiratory arrest and death. Fentanyl withdrawal symptoms include anxiety, irritability, dysphoria, sweating, diarrhea, tremors, and abdominal cramps [9]. The duration and severity of these withdrawal symptoms vary and depend on chronicity, the potency of the opioid in use, and individual variability. Some people may have relatively mild symptoms, while others may have severe symptoms that could last several days requiring close medical attention [12].

Fentanyl is metabolized mainly in the liver (N-dealkylation) via the CYP3A4 isoenzyme to inactive norfentanyl. Life-threatening interactions occur when fentanyl is mixed with alcohol or cocaine. Fentanyl and alcohol exert a synergistic depressive action on the cardiovascular system while cocaine does the opposite, causing excitation, resulting in cardiac arrhythmia. Physicians should be aware of drug-drug interactions in giving pain medications such as fentanyl when prescribed with other medications (Table 1) [9].

Table 1: Common drug-drug interactions of fentanyl with other medications

Pain medications	Interacting drug	Adverse outcome
Morphine, Fentanyl	Anticholinergic drugs	Synergistic: urinary retention, constipation
Morphine, Fentanyl	Benzodiazepines	Synergistic: hypotension, Respiratory depression
Morphine, Fentanyl	Muscle relaxants (e.g., baclofen and others)	Respiratory depression
Fentanyl	CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir)	Prolongation of fentanyl effects
Fentanyl	CYP3A4 inducers (e.g., phenytoin, ethosuximide, carbamazepine)	Decreased efficacy of fentanyl
Morphine, Fentanyl	MAOIs (e.g., phenelzine and others)	Synergistic: hypertension, significant respiratory depression
Fentanyl	Neuroleptics	Synergistic: hypertension
Fentanyl	Nitrous Oxide	Synergistic: CVS depression
Morphine, Fentanyl	Serotoninergic drugs	Synergistic: serotonin syndrome
Morphine, Fentanyl	TCAs (e.g., amitriptyline, nortriptyline)	Prolongation of morphine or fentanyl effects

Note: CYP3A4, cytochrome P450 3A4; MAOI, monoamine oxidase inhibitors; CVS: cardiovascular; TCAs, tricyclic antidepressants

Fentanyl may be misused in the form of oral pills, lozenges, wearing patches or injecting intravenously. The powder form is snorted and smoked, whereas patches can also be taken sublingually or injected. Patients with mental illness or a family history of substance abuse have an increased risk of opioid addiction [1].

The Objectives of This Review Paper are:

1. To find out the causative factors of increased mortality from opioids
2. To find out the available resources, current treatments and educating physicians and psychiatrists about fentanyl overdose
3. To describe future directions of treatments.

Methods

A literature search using the PubMed database was conducted. Keywords used were "opioid addiction" or "fentanyl abuse," and "fentanyl overdose," and "fentanyl treatment." This resulted in 310 articles. Twenty articles relevant to our topic were chosen. Additional twelve references were gathered from the Centers for Disease Control and Prevention, Physicians' Desk Reference, American Psychiatric Association, National Institute on Drug Abuse, and other websites. Further, our case report highlights the consequences of fentanyl abuse in combination with other substances. Our patient stated using fentanyl by extracting it from fentanyl transdermal patches and injecting intravenously to get high, as described below.

Case Report

A 31-year-old Caucasian female with a history of polysubstance use, bipolar II disorder (most recent episode depressed), PTSD, and hepatitis C was admitted to ICU for community-acquired pneumonia following overdose with fentanyl, heroin, and cocaine. The patient received multiple doses of naloxone by the EMS before arrival to our ED. Our case represents the intravenous way of abusing fentanyl and describes the serious consequences of combining it with other drugs by opioid users.

The patient was reportedly collecting the fentanyl transdermal patches prescribed to others; extracting and injecting it intravenously. She stated to have tried to wean off from fentanyl by using methadone (30 mg per day), prescribed originally to her friend. The patient also had a history of chronic heroin (5-10 bags per day) and cocaine (2 grams per day) use. Urine toxicology came positive for heroin, cocaine, fentanyl, and methadone.

During the detox process, the patient was given 20 mg methadone but was discontinued the next day as the patient developed hypotension and pinpoint pupils. Home medications quetiapine and fluoxetine were discontinued. Cardiac workup showed infective endocarditis with tricuspid vegetation requiring surgical intervention. She developed further complications, including respiratory failure requiring prolonged intubation followed by tracheostomy. She also developed acute kidney injury followed by chronic renal failure treated with hemodialysis. After two months of hospital stay, she was discharged home on trazodone. The patient did not keep her follow up appointments with psychiatry and medicine outpatient clinics.

The patient stated to have been sexually abused by her male babysitter from the age of 7 to 15. She started using drugs at 17 years of age. Although she managed to earn an associate degree, she never got a job due to the consistent use of drugs to get high. She became homeless and started rotating between her friends and families. She lost custody of her two children (four and five years old) to her mother due to obvious drug issues. The patient tried to become sober multiple times in the past to get custody of her children but was unable to do so.

Results

Fentanyl is often mixed with other substances and sold as heroin to unsuspecting users [9]. Its abuse may cause life-threatening respiratory failure from an overdose [1]. The treatment for the overdose is naloxone [10]. Complications of polysubstance use might include pneumonia, respiratory failure, infective endocarditis, renal failure, septic shock, and coma, which could be fatal.

Discussion and Conclusions

Fentanyl description as an analgesic and euphoric agent:

Fentanyl is a strong agonist at mu- and kappa-opioid receptors. It is not only used with general, regional, and spinal anesthesia but also used for acute, chronic, breakthrough, and neuropathic pain [14, 15]. Analgesia is mediated through changes in the perception of pain at specific regions in the spinal cord and the CNS. Binding of fentanyl to mu- and kappa-opioid receptors in those regions stimulates the guanosine triphosphate (GTP) which decreases intracellular cyclic adenosine monophosphate (cAMP) by inhibiting adenylate cyclase that modulates the release of nociceptive neurotransmitters such as substance P, gamma-Aminobutyric acid (GABA), dopamine, acetylcholine, and norepinephrine. The stimulatory or euphoric effect of fentanyl is through its agonist action on mu-opioid receptors, which results in inhibition of the release of inhibitory neurotransmitters such as GABA and acetylcholine. Opioid agonists exert both analgesic and euphoric effects probably because of differential susceptibility of the opioid receptor to desensitization or activation of more than one G-protein system or subunit by an opioid receptor [1].

Dependency

Drug use is defined as the use of a drug consistent with legal or medical guidelines. It becomes misuse when the use is inconsistent with the prescribed dosage or frequency. It turns into abuse when chronic use begins impacting specific aspects of life, including health [16]. Substance abuse can be considered as the initial step leading to substance dependence. Dependence is the repeated use of a drug or chemical, with or without physical or psychological dependence. Physical dependence is an altered physiological state caused by repeated use of a drug which results in a specific withdrawal syndrome upon discontinuation or dose reduction of that drug [17]. Psychological dependence is an emotionally conditioned response to triggers such as events, places, or anything a person associates with while using a substance which provokes a strong desire to reuse that specific substance [18].

The dependence on a substance is different from addiction. Both prescription treatment, as well as abuse of a substance, may cause dependence. It presents with the appearance of withdrawal symptoms when the use of tolerance forming substances like fentanyl or opioids is suddenly discontinued after long-term use. The specific symptoms may include diarrhea, abdominal cramps, body aches, shivers, sweating, anxiety, irritability, and dysphoria [7, 12]. Dependence can cause opioid-seeking behavior as the person resists these uncomfortable withdrawal symptoms upon discontinuation of the opioid. This repeated exposure to the opioid in question finally results in addiction [12]. Addiction marks changes in specific brain regions such as basal ganglia, extended amygdala, and prefrontal cortex (Figure 2).

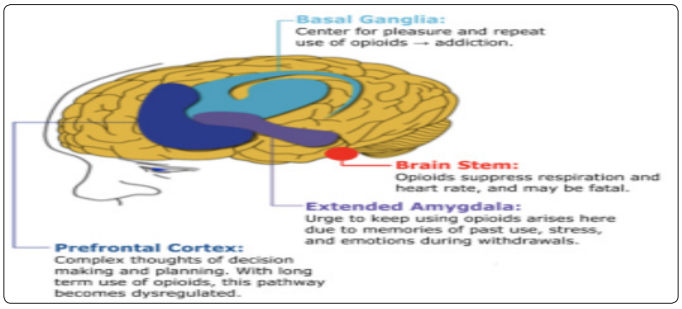

Figure 2: Drugs of abuse alter basal ganglia, extended amygdala, and prefrontal cortex resulting in compulsive drug use that marks the addiction [19]

The National Institute on Drug Abuse (NIDA) describes addiction as a chronic, relapsing disorder represented by drug-seeking behavior and use that is compulsive, despite harmful consequences. It may occur as a result of CNS rewarding (euphoric) effects and relief from pain in patients using it either illicitly or as a prescription medication for pain. These behavioral changes reflect long-lasting changes in brain function, particularly in the brain's inhibition and reward centers. The DSM-5 does not use the term addiction, but NIDA's description of addiction corresponds closely to the DSM-5 definition of substance use disorders at the severe end of the spectrum [20].

Presentation

The typical clinical presentation of opioid overdose is characterized by a triad of pinpoint pupils, unconsciousness, and respiratory depression. Fentanyl overdose begins suddenly (within seconds to minutes), and can present with atypical physical symptoms such as blue discoloration of the lips, stiffening of the chest and body, seizure-like activity, foaming at the mouth, and strange affect before becoming unresponsive [7, 21]. Intravenous administration of fentanyl can result in life-threatening respiratory depression within two minutes [22].

Treatment (Emergency and Long Term)

Naloxone, a short-acting opioid receptor antagonist, is used for emergency treatment of opioid overdose [23]. It is available as a solution for intravenous, intramuscular, subcutaneous, orotracheal injection, and as a nasal spray. The recommended initial dose is 2-4 mg intranasal or 0.4-2 mg subcutaneously/intramuscularly or 0.04 mg intravenously, to be repeated every 2-3 min, as needed, up to 10 mg [9]. Auto-injectable naloxone have proven to be life-saving in case of an opioid overdose before the arrival of emergency medical care. Strategies that are under research to manage opioid overdose induced respiratory depression include phrenic-nerve-stimulation devices, 5-hydroxytryptamine 1A agonists, and ampakines [24].

In the case of fentanyl overdose treatment, universal precautions of wearing gloves and mask must be used due to its high potency and rapid absorption. Of equal importance is the administration of oxygen and chest compression to counteract chest wall rigidity [25]. Fentanyl overdose is reversed with prompt, multiple (as many as six times) dosages of naloxone, up to 12 mg [26]. Similarly, an opioid when combined with other substances having a synergistic effect, requires higher than optimal doses of naloxone for overdose reversal [9].

Long-term treatment of opioid abuse to reduce cravings and withdrawal symptoms include methadone, buprenorphine, and naltrexone. However, in the case of fentanyl abuse, current data suggests that these agents may be less effective in treating fentanyl abuse than they are in treating other opioid abuse [10].

Prevention

To prevent abuse, the lowest effective dose of the opioid should be prescribed. The total number of opioid prescriptions dispensed is still high, with a total number of 191, 218, 272 prescriptions given in 2017 [27]. It is imperative at this time to reduce inappropriate prescription of opioid medications. Other recommendations are to prescribe tamper-deterrent formulations, combinations of agonist and antagonist, sequestered aversive agents, pro-drugs and novel delivery systems. Screening tools to identify potential patients at risk include Current Opioid Misuse Measure, Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain, and Brief Risk Interview [9]. The Brief Risk Interview is a much more efficient predictor of behavioral changes in comparison to other screening tools [28]. Furthermore, there are schemes to monitor problematic use including urine drug testing, medication counts, and blood level monitoring [9]. Additionally, conjugate vaccines against fentanyl and its analogs' use are under research. Tapentadol needs a special mention as it is an FDA approved analgesic with a dual mechanism of action, combining mu-opioid receptor agonism with noradrenaline reuptake inhibition. This mechanism is responsible for its opioid-sparing effect, which contributes to a reduction in adverse effects such as significant respiratory depression with opioids, and may result in improved safety and compliance [29]. This combination of analgesia and tolerability contributes to a major improvement over current pain treatment regimens and is a valuable addition to the analgesic medicines.

Rehabilitation

The Harm Reduction Coalition (HRC) surveyed 140 organizations in the US from 1996 to 2014, which were known to provide naloxone kits to laypersons. As per the survey, the organizations distributed naloxone kits to 152,283 laypersons and reported 26,463 overdose reversals [30].

"RELAY" Program (June 2017; 1-833-337-3529) is part of the New York City Department of Health and Mental Hygiene's Healing NYC initiative to reduce the opioid overdose epidemic through a harm reduction approach. It has advocates who reach the participating hospitals within an hour of being called in by the department after a non-fatal patient overdose. The advocates provide opioid overdose risk reduction counseling and rescue training and connect them with suitable services. They stay in contact with the patient for up to 90 days. Additionally, the patient is provided with a naloxone nasal spray kit with two doses to help reverse any future events. As a routine, one should give one dose of naloxone right away in suspected overdose and wait two to three minutes; if it does not work, then the second dose is administered. Until November 2018, the program has worked with 620 overdose survivors and provided 913 naloxone kits [31].

Narcotic Anonymous (NA), founded in 1953, is a 12-step program, which like any other self-help group program, provides a safe, supportive, and non-judgmental environment for patients to discuss their vulnerabilities regarding use, relapses and their recovery; and connect with sponsors who have gone through similar struggles and were successful. In many aspects, it is an extension of drug addiction treatment. There are meetings in groups all over the country to help make the NA encounter more reachable to all those who need it [32].

We conclude that there is a need to strengthen communication between public health and public safety agencies for better surveillance and to provide rapid response in high-risk places. It is prudent to improve overdose detection of fentanyl and its analogs, increase accessibility to naloxone, assure maximum utilization of harm reduction techniques, and to have adequate medication-assisted treatment facilities [24].

More treatment centers equipped with well-trained personnel and easy availability of naloxone are needed to treat cases of fentanyl overdose efficiently. It has been observed that persons using fentanyl have a better chance of surviving an overdose if spotted by someone trained and equipped with sufficient doses of naloxone. In countries like Canada and Australia, overdose morbidity and mortality rates have dropped in areas near the supervised injection facilities where trained staff spots overdose, and administer naloxone promptly [21]. Additionally, research should focus on the pain medications that are safe with less addiction potential and fewer side effects.

Scientific Significance

Prescribers have a role in reducing opioid overdose deaths by checking online for Prescription Drug Monitoring Program (PDMP) and testing for drug abuse as well as prescribing the lowest,

effective, and shortest duration of treatment. It is worth to consider alternative options such as acupuncture, transcutaneous electrical nerve stimulation (TENS) therapy, bioelectric therapy, physical therapy. These methods may not replace but might decrease the need for pain medications. Further, insurance policies should cover these alternative options for all those who seek pain medications.

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