Reasons to avoid fentanyl

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Abstract: Fentanyl has been FDA approval as an analgesic since 1968 and multiple different fentanyl preparations have been developed over the years. Little was known about it is clinical utility defined by risks and benefits until recently. Present commercially available preparations are easily tampered and nonpharmacologic fentanyl has become the major cause of opioid deaths in the United States. This state-of-the-art review will discuss fentanyl pharmacology, utility, safety and abuse.

Keywords: Fentanyl; utility; respiratory depression; wooden chest syndrome; substance abuse

Introduction

In 1960 Janssen developed parenteral fentanyl which received FDA approval in 1968. In 1990 transdermal fentanyl became available for opioid tolerant individuals and in the 1990's and beginning in 1998 a series of rapid-acting transmucosal fentanyl products became commercially available for breakthrough pain (1-3). Parenteral fentanyl went off patent in 1981 and sales thereafter skyrocketed 10-fold over the next 10 years (4). A REMS program of education and monitoring was developed for rapid-acting fentanyl commercial products in light of reports of rising fentanyl use outside of licensing guidelines and indications. It is only recently that we have learned about the unique fatal nature of fentanyl which presently dominates the opioid crisis (1,5). In 2011 oxycodone was the major opioid leading to overdose deaths following the development of tamper resistant formulations of extended release oxycodone heroin became the primary culprit between 2012–2015. The latest data from the National Vital Statistics System revealed that in 2017 more than 28,000 deaths were a result of synthetic opioids (other than methadone) and according to the reports fentanyl was the main driver for these overdose deaths, largely derived from non-pharmaceutical

sources (6-10). Studies by the Leiden group published in 2013 demonstrated the narrow utility of fentanyl described as a relationship between the dose at which analgesia occurs and the dose at which respiratory depression is seen (ED50 analgesia-TC50 respiratory depression) (11). Rapid deaths occur due to the "wooden chest syndrome" (WCS) which consists of a combination of rapid muscle rigidity and laryngospasm (12). Anesthesiologists have been aware of the WCS but it is relatively unknown within the medical community (13-15). The WCS has also been described with the other lipophilic opioids, sufentanil and alfentanil (16-18). Deaths occur so rapidly that norfentanyl is not detected in plasma at postmortem examination (19). The WCS is not reversed by naloxone which may worsen rigidity and laryngospasm through release of norepinephrine in opioid tolerant individuals (20-23). Unlike morphine and oxycodone which in low to moderate doses increases brain oxygen levels through neurovascular compensation, fentanyl produces a dramatic reduction in brain oxygen levels (24). When fentanyl is added to heroin, the combination produces a greater reduction in brain oxygen levels relative to either fentanyl or heroin alone (24,25). Morphine reduces respiratory rate but not tidal volume whereas fentanyl reduces both tidal volume and respiratory rate (25).

There is also non-cross tolerance to respiratory depression between morphine and fentanyl (25).

The risk of overdose in the population with fentanyl is twice that of heroin and 8 times greater than that of other opioids (26). The odds ratio of a family member having an overdose on a non-fentanyl opioid product is 2.9 fold but it is 4.3-fold if transdermal fentanyl is prescribed to a family member (27). Emergency department survival is lower with fentanyl and admission rates higher relative to heroin overdoses (28). Transdermal fentanyl is highly abusable and is not tamper resistance. Fatalities occur with single doses of 2 mg and at the end of a 3-day period there is 0.7–1 mg of fentanyl found in a 25 micrograms/hour patch and 4 mg or more in 100 micrograms/hour patch. The matrix patch is easily tampered with recipes available on darknet websites with extraction rates of 100% and is preferred to reservoir patches (29-32). Reversal of fentanyl overdoses requires an average of 3.6 mg of naloxone which is much higher than that required for morphine or heroin (33). Rapid-acting fentanyl products have been reported to be statistically better than oral immediate release opioids for breakthrough pain for cancer patients. However, the responses are not clinically meaningful with a number needed to treat (NNT) of greater than 10 for the primary outcome and with Bayesian likelihood ratios <5 (34-37). Rapid-acting fentanyl products are not cost effective (37). This review will outline pharmacological reasons as well as clinical reasons for limiting the use of fentanyl in clinical practice.

Why is fentanyl a dangerous opioid relative to other opioids?

Metabolism

Fentanyl metabolism plays a minor role in its utility. Fentanyl is biotransformed in the liver by the mixed function oxidase CYP3A4, principally to norfentanyl which is an inactive metabolite. There are also minor metabolites produced by other pathways all of which are inactive. Small amounts of the parent drug, ranging from 8–10%, are cleared by the kidneys and gastrointestinal tract (38,39). Fentanyl, alfentanil and sufentanil are recommended in patients with renal impairment based on pharmacokinetics and clinical experience. However, a systematic review found very little clinical evidence for this (40). Marked decreases in fentanyl clearance does occur in patients related to very high BUN concentrations (41). Fentanyl pharmacokinetics are adversely influenced by liver disease and certain drugs

which interact with CYP3A4 (macrolides, first generation selective serotonin reuptake inhibitors, certain azole antifungals, certain HIV medications among other drug classes) (42,43). Fentanyl and fentanyl analogues are not routinely tested by standard immunoassay urine toxicology screens but require gas or liquid chromatography mass spectroscopy for detection. Newly developed immunoassays of fentanyl have not been validated (42). Clinical analgesic doses produce plasma levels of 0.3–0.7ng/mL; doses greater than 3 ng/mL cause loss of protective airway reflexes and CNS depression (44,45).

Utility function and fentanyl safety

A measure of fentanyl safety is its utility function. The concept of utility function was originally developed in economics but later adapted by Steiner in 1978 into the discipline of pharmacology (46). In context, utility function is a mathematical model which weighs analgesia and toxicity (respiratory depression) over time using an equation that provides a single number at each time point which can be either positive or negative as it reflects the benefits of analgesia (+) versus respiratory depression (–) (11). In humans, utility function has been measured by comparing doses, plasma levels and response to experimental pain and respiratory responses to standardized end-tidal CO_2 (ETCO$_2$). Utility function differs from the therapeutic index which is a ratio of the dose at which toxicity is observed (TD50) to the dose at which analgesia is experienced (ED50) (47). The higher the number the better the therapeutic index. The therapeutic benefits and toxicities involve different mechanisms which should be measured separately. Response to plasma level changes overtime are such that utility function will change over time as plasma levels rise and fall. Responses whether therapeutic or adverse may not be parallel plasma drug levels nor doses. Utility function may differ depending on the type of experimental pain and the toxicity used in observation. Respiratory depression has almost uniformly been chosen as the outcome toxicity due to its associated mortality (47).

In a study by Boom and colleagues, fentanyl at a dose of 3.5 µg/kg was used to test analgesia to electrical pain on one day and changes in minute ventilation responses to a standardized ETCO$_2$ level over time on the following day. Pharmacokinetics and pharmacodynamics were determined using a 25% reduction in pain intensity (ED25) as one outcome and 50% reduction in minute ventilation to standardized ETCO$_2$ (TC50) as the other outcome (11).

The utility function was defined the probability of a 50% reduction in pain intensity compared with the probability of a 50% reduction in minute ventilation with the standardized $ETCO_2$ over time. At low fentanyl doses which produced plasma levels less than 0.7 ng/mL, a positive utility function was observed. At higher plasma levels the utility function became negative. Boluses of fentanyl had an initial negative utility function in the first hour. There were some criticisms of this model. The clinical relevance of minute volume responses to $ETCO_2$ is not established. Data was dichotomized which reduces sensitivity. There may be different sensitivities to different endpoints. Electrical pain may be relatively resistant to opioids and the use of other pain mechanisms for analgesia may produce a more positive utility function(47). Nevertheless, this is a step forward in considering equitoxicity and equianalgesia. In an earlier study with a slightly different method in animals , the utility function of buprenorphine was found to be dramatically different and positive relative to fentanyl in an animal model (48). Even though fentanyl and buprenorphine equianalgesia is nearly 1 to 1, the safety of buprenorphine was far superior to fentanyl as demonstrated in this model (48,49).

In a study by the same group that looked at alfentanil (a lipophilic opioid similar to fentanyl) in human volunteers, there was only a 40% chance of getting a 50% reduction in pain intensity without causing respiratory depression (50). Put in a little different way, using a lipophilic opioid like fentanyl or alfentanil there is a 70% chance of having a 25% reduction in pain severity without respiratory depression but the probability of reducing pain intensity by 50% without respiratory depression is less than 50% (51).

Fentanyl influences on minute ventilation

Minute ventilation is a combination of respiratory rate and tidal volume. The effects of fentanyl on the respiratory system are a decrease in peripheral and central chemoreceptor gains in ventilation and a direct inhibition of respiratory neural activity (52). CD-1 mice exposed to morphine and heroin have a reduced respiratory rate but not tidal volume whereas fentanyl simultaneously reduces both respiratory rate and tidal volume (25). The more rapid reduction in minute volume associated with fentanyl was caused by a rapid reduction in tidal volume not seen with the other opioids. Fentanyl was 70-fold more potent than heroin in reducing minute volume. Higher doses of naloxone were required to reverse fentanyl respiratory

depression relative to equianalgesic doses of heroin and morphine. In addition there was a relative non-cross tolerance to respiratory depression between morphine and heroin to fentanyl (25).

Fentanyl and brain hypoxemia

Cerebral hypoxemia can occur with opioid exposure which is related to respiratory depression and may be countered by compensatory neurovascular dilatation. Non-neuronal effects of opioids include involve cerebral blood flow and direct effects on the cerebral vasculature such as altered vascular reactivity (53). In one study, Long-Evans rats exposed to heroin, fentanyl, oxycodone and morphine were tested for nucleus accumbens (mesolimbic) hypoxia (24,54,55). Subcutaneous oxygen levels were measured which directly reflects respiratory depression. Heroin in low doses (0.1 mg/kg) reduced brain oxygen levels by 30% and in doses commonly used on the street, by 50%. Brain hypoxia occurred within 3–4 minutes in these opioid naive animals and was largely due to respiratory depression. The metabolite monoacetylmorphine was responsible for brain hypoxemia (24). Fentanyl like heroin, rapidly decreased brain oxygen levels largely due to respiratory depression. However, fentanyl was 10–20-fold more potent in doing so. The combination of fentanyl and heroin in equianalgesic doses to monotherapy dramatically reduced brain oxygen levels for a prolonged period. The area-under-the-curve for oxygen deprivation was 10-fold greater than fentanyl alone and 5-fold greater than heroin alone in equivalent doses to the combination. In contrast, oxycodone at low to moderate doses (0.3–0.6 mg/kg) increased nucleus accumbens oxygen levels through compensatory neurovascular responses. At higher doses (1.2 mg/kg) there was a biphasic response with transient hypoxia. Morphine, like oxycodone, in doses between 0.1 and 1.6 mg/kg increased brain oxygen levels but decreased at a much higher dose level (6.4 mg/kg) caused brain hypoxia. At these high doses respiratory depression overwhelmed neurovascular compensation (24,54-56).

The wooden chest syndrome

The manifestations of the WCS are muscle rigidity, seizure-like behavior, cyanosis and loss of consciousness within minutes of fentanyl injection (57). Physiologically the chest wall and diaphragmatic muscle become rigid with simultaneous laryngospasm which makes it difficult to impossible to intubate the person. The WCS can occur with

any route of fentanyl administration and its frequency is dose dependent; it is also dependent on speed of delivery (58). Laryngospasm is caused by central activation of the recurrence laryngeal and external superior laryngeal nerves which control laryngeal abductors and adductors (59-61). The adductors, lateral cricopharyngeus and transverse arytenoid muscles, are activated by a sympathetic innervation and norepinephrine release while the abductor, posterior cricoarytenoid muscle, is inhibited (59-61). Motor neurons to adductors increase firing rates within 20 seconds of fentanyl injection (59). Fentanyl increases tracheal pressure which is blocked by droperidol, a potent alpha-1 adrenergic receptor blocker (23). Laryngospasm is almost exclusively reported with lipophilic opioids (18,23). Naloxone does not reverse laryngospasm (62,63). In the operating room succinylcholine has often been often used to block the WCS (23).

Chest wall rigidity with fentanyl was noted both early in its use and was noted to occur sporadically with relatively low doses (0.5 micrograms/kilogram IV) but with regularity at higher doses (greater than 10 µg/kg). Rigidity becomes clinically evident within 2 minutes of injection and will last on average 15 minutes (58,64-68). On the streets, fentanyl deaths are noted to occur so quick that at postmortem examination half of individuals do not have detectable norfentanyl in plasma suggesting that they died of the WCS rather than of respiratory depression (which occurs later) (19). Fentanyl freely and rapidly penetrates the blood-brain barrier and not only binds to mu receptors but also alpha-1 adrenergic receptors within the locus coeruleus releasing norepinephrine (22,69-72). It is now known that the sites within the CNS and the receptor populations responsible for the WCS are distinctly different from the receptor populations and sites responsible for respiratory depression (73). As a proof of concept that the alpha-1 adrenergic receptor is the cause of the WCS, the alpha-1 adrenergic receptor antagonist prazosin prevents fentanyl WCS in animals (22,72). As mentioned before droperidol, a dopamine receptor antagonist but also a strong alpha-1 adrenergic receptor blocker decreases chest wall rigidity and laryngospasm (74,75).

Through binding to alpha- 1 adrenergic receptors within the locus coeruleus, fentanyl "disinhibits" norepinephrine neurotransmission (76,77). Fentanyl also increases norepinephrine release by increasing glutaminergic neurotransmission (21,71). However, this is not a major cause. Ketamine only partially reverses fentanyl rigidity but allows for normalization of oxygen and carbon dioxide

levels in rats (78). Muscle rigidity is seen in multiple muscles including the gastrocnemius, abdominal rectus and sacrococcygeal dorsalis lateralis muscle (22,72).

There are two other minor mechanisms by which norepinephrine is released by fentanyl. Fentanyl blocks GABAergic inhibitory neurons within the locus coeruleus which results in increased norepinephrine release (79,80). Fentanyl, unlike morphine, is a norepinephrine reuptake inhibitor which increases norepinephrine within synapses (38,81).

Fentanyl modulates cholinergic neurotransmission in medullary motor centers which controls respiratory mechanics and airway patency (22,74,82-84). Cholinergic activation influences coronary, hepatic and cerebral perfusion resulting in diminished perfusion at all three sites (54,85,86). This may account for an unusual fentanyl overdose presentation of chest pain and bradycardia (58).

As mentioned previously, naloxone can worsen the WCS (23). Rapid injections of naloxone particularly in opioid tolerant individuals cause a release of norepinephrine resulting in pulmonary edema, laryngospasm and cardiac an arrhythmia (87). Naloxone does not reverse fentanyl induced laryngospasm (23,88-91).

Transdermal fentanyl safety

Many would consider transdermal fentanyl a convenient opioid and relatively safe to use which has the benefits of increased compliance (92,93). However its use has been reported to be unsafe. Fentanyl initiation was reported to be unsafe in 74.1% of patients because prior opioid exposure was inadequate based on FDA licensing standards (94). Transdermal fentanyl is a very tamper-prone prescription products. There are reported increased number of deaths in Canada with fentanyl many of which are from a nonpharmacological sources however, half the deaths from a report published in 2006 were from transdermal fentanyl (95,96). Mean fatal fentanyl plasma level in this group of patients was 15 ng/mL (range 3 to 71 ng/mL). The authors noted an overlap of fentanyl plasma levels between those who were felt to have died from natural causes and those who were felt to have died from a fentanyl overdoses. Half of the deaths were from fentanyl alone while the other half were from polypharmacy. Polypharmacy included alcohol or other opioids mostly oxycodone or morphine. Ten percent were related to drug interactions most frequently involving selective serotonin reuptake inhibitors which delay fentanyl clearance. Males were more likely to die from illicit IV

fentanyl injections either derived from the transdermal patches or acquired from non-pharmacological sources. At postmortem examination there was incomplete distribution of fentanyl from femoral blood to heart indicating rapid deaths (96).

In certain parts of the world overdose deaths from fentanyl are largely from transdermal patches (97,98). The matrix patch is actually preferred by those who abuse fentanyl since the fentanyl is easily extracted from matrix patches (29,32,98-101). Online recipes for extracting fentanyl can yield 100% of the fentanyl from a patch within 25 minutes (98). However, it is difficult for those extracting fentanyl from transdermal patches to know the amount of fentanyl in the extracted liquid such that injections are quite risky. Often times stored fentanyl extracts are shared resulting in a high incidence of HIV infections and hepatitis C (99,102). Those who abuse fentanyl patches often have a police record for drug abuse (72%), own drug paraphernalia (69%), and have fresh or old puncture marks found on their body (81%). The typical age is 35 years and 82% are males. The average plasma level at postmortem examination is 16.9 ng/mL. Blood levels of diazepam, pregabalin, alcohol, methadone, morphine and cocaine are found in half of individuals (97,100,103). In a subset, fentanyl patches will be found in the mouth either against buccal surfaces or chewed, in the airway or stomach. A number will not be found to have puncture marks and are assumed to have used intranasal fentanyl or relatives or friends have removed patches before authorities arrived (57,104-111). Other routes of abuse include vaping extracts or patches, e-cigarettes and smoking patches (112).

The amount of fentanyl remaining in a patch after 3 days of use is significant. There is between 0.7–1.22 mg of fentanyl left after 3 days in a 25 µg/hour patch and between 4.5 and 8.4 mg of fentanyl left in a 100 µg/hour patch. A single lethal dose of parenteral fentanyl is 2 mg (113,114). The standard transdermal route produces less euphoria than morphine or heroin but the rewarding effects are magnified several fold by IV injection, intranasal administration, heating and vaping patches and in e-cigarettes (95,114). The transdermal fentanyl patch is an easy commercial product to tamper.

Deaths have occurred with legitimate transdermal fentanyl use. Prescribers have started patients who are opioid naive on 50–100 µg/hour patches. Deaths occur at the change to the second patch in this group. Adolescents may diversion of a single 50 µg/hour patch originally prescribed to a family member who is unaware of the diversion. The odds of an overdose within the family of a patient prescribed transdermal fentanyl is 4.3 whereas the odds of an overdose with an extended release opioid is 2.9 (27). Deaths have occurred in individual started on transdermal fentanyl who are also on medications which strongly inhibit CYP3A4 (115).

The FDA has issued a warning about the use of fentanyl patches in patients who are not opioid tolerant (defined as 7 days of morphine 60 mg a day, oxycodone 30 mg a day or hydromorphone 8 mg a day) (42). It is not unusual opioid naive patients to be started on transdermal fentanyl at a dose of 25 micrograms/hour which is equivalent to 60 mg of oral morphine daily (116). Adherence to the licensing guideline is only 50% (117).Transdermal fentanyl is not a good opioid to use in patients who are both opioid naïve and in acute pain even though the 12.5 µg/hour patch has been used in this population (70,118).

The proportion of patients who enter the emergency department with a fentanyl overdose and who either die or are admitted is much higher than that seen with heroin. There is a narrower naloxone response time window for reversing fentanyl overdoses and much higher naloxone doses are required to reverse fentanyl overdoses than with heroin (28).

Several extended release opioids have been made tamper-resistant by adding naloxone which has a high first pass clearance or are formulated with naloxone or sequestered naltrexone which is released only if the preparation is damaged chewed or grinded (119,120). Naloxone and naltrexone are both absorbed through the skin such that it would not be feasible to place either drug within a transdermal matrix to produce a tamper resistant transdermal patch (121-125). Both antagonists would need to be sequestered to prevent transcutaneous absorption.

Rapid-acting fentanyl and cost effectiveness

The rapid-release fentanyl products consist of buccal tablets, sublingual tablets, buccal film, intranasal spray and oral transmucosal fentanyl citrate. The sublingual tablets are administered directly under the deepest part of the tongue. The disintegrating tablet rapidly falls into small particles, the particles are not to be swallowed. The sublingual tablet has fentanyl on its outer layer which is absorbed in about 30 minutes. The tablet can be swallow thereafter. The oral transmucosal fentanyl citrate is moved around in the mouth and sucked but not swallowed while the fentanyl in the sugar matrix is absorbed through the mucosal lining.

The effervescent buccal tablet has a low pH which keeps fentanyl in a non-ionized state allowing rapid absorption of fentanyl through the mucosal surface. It is placed back above the rear molar tooth. The fentanyl buccal film has fentanyl embedded in a small biodegradable polymer film. The sachet is opened prior to use and the tongue used to moisten the area of application on the buccal mucosa prior to placing the film. Intranasal fentanyl spray has fentanyl in a phosphate buffered solution which is sprayed into the nasal cavity. There are single and multiple dose devices. A second nasal spray contains pectin , droplets of the product form a gel on the nasal mucosal surface (126). How do these fentanyl produces compare clinically with oral immediate release morphine and oxycodone? As a outcome which defines a response, rapid-acting fentanyl (and opioids in general) clinically must reduce pain intensity by 33% and 50% using a numerical rating score (127). The proportion of responders to fentanyl are compared to the proportion of responders to placebo in placebo controlled trials. The number needed to treat which gives clinicians a sense of efficacy which is 100 over the differences in response rates between the experimental therapy and the comparator. The NNT is a form of a "responders analysis" of the patients who benefit from experimental therapy relative to controls or standard treated patients. High numbers demonstrate small differences and low efficacy. The number needed to treat is the number of individuals who would need to be treated with the experimental therapy (in this case fentanyl) instead of the comparator (in this case placebo) in order to benefit one additional individual relative to the comparator (128-131). A good NNT for symptoms should be in single digits (131). At 15 minutes the number needed (NNT) relative to placebo for fentanyl is 5 using a 33% reduction in pain intensity as an outcome and 14 when using a 50% reduction in pain intensity (132). Benefits of an intervention need to be balanced against cost. Financial harms to patients or society are not often included in trials. Harms must be weighed by side effects and drug misuse which are indirect costs to society and patients. In regards to misuse, in randomized trials of rapid-acting fentanyl products which included the rigors of screening for addiction, drug monitoring and universal precautions, the prevalence of fentanyl misuse is around 11% (133,134). Positive urine toxicology is no higher than for the comparator immediate acting opioid (133).

Several studies have compared rapid-acting fentanyl with an oral immediate release opioid. One study compared fentanyl pectin nasal spray with immediate release morphine. The NNT at 15 minutes for a 33% reduction in pain intensity was 12.3 and at 10 minutes it was 17.8 compared to morphine (34). In a second study which compared fentanyl buccal tablets to immediate release oxycodone, the NNT at 15 minutes for a 33% reduction in pain intensity was 25 compared to oxycodone (35). The indirect differences between oxycodone and morphine may be related to the fact that oxycodone is selectively transported across the blood brain barrier (135,136). A third study compared sublingual fentanyl citrate tablets to oral morphine elixir for breakthrough pain over 30 days. The mean fentanyl does was 235 mcg and oral morphine dose 38 mg. There was no open label titration prior to randomization unlike the previous two studies. The mean pain intensity differed between the groups favoring fentanyl at 3, 7, 15 and 30 days. The onset to analgesia with fentanyl was noted to be 5 minutes and for morphine 15 minutes at 30 days. The differences in pain intensity was 1.4 points on a 0 to 10 numerical rating scale favoring fentanyl but the timeframe to response and the number of responders in each group was not be determined (137). A meta-analysis using Bayesian credible limits indirectly compared the likelihood of superiority of fentanyl to morphine for breakthrough pain. It is important to understand that comparisons were indirect, across trials. A likelihood of superiority of 67% has a Bayes factor of 2 and 75% a Bayes factor of 3. In general, a Bayes factor <5 is considered weak evidence (138). The likelihood for morphine compared to placebo was 56%, for the oral disintegrating fentanyl tablet it was 66%, for oral transmucosal fe4ntanyl citrate it was 73% and for fentanyl buccal tablets it was 83%. Hence the superiority of fentanyl over oral morphine by indirect comparisons is weak except perhaps for the buccal tablets. It is likely to be weaker when compared to oxycodone.

Drug related financial toxicity is a major and growing issue. By comparing prices in GoodRx (11/12/2019), fentanyl buccal tablets(#60 CVS pharmacy) costs over 4,000 US dollars whereas in the same national pharmacy center immediate release oxycodone [#60 (30 mg)] costs 55US dollars and morphine [#60 (30 mg)] cost 20 US dollars. The lack of affordability to patients and out of pocket expenses for co-pays for patients for rapid-acting fentanyl makes these products a last resort (37). This is recommendation is consistent with the National Institute for Health and Clinical Excellence: Guidance on opioids in palliation (139). The abuse potential of these products on the streets should be a consideration when prescribing. Universal precautions should be practiced as with all opioid therapy.

There has been a consistent violation of FDA Risk Mitigation Strategies (REMS) in prescribing rapid-acting fentanyl products (140). In a report from a qualitative analysis of 4,877 pages of FDA documents, 11.6% a prescribers wrongly thought that rapid-acting fentanyl products could be used in opioid naive patients. At 60 months after product release, between 35% and 55% of patients on rapid-acting fentanyl products were not opioid tolerant by the FDA definition described in the REMS. At 48 months, over 1/3 of patients on rapid-acting fentanyl had chronic non-cancer pain which is contrary to licensing agreement. Even at 60 months nearly 20% of prescribers and nearly half of patients felt that rapid-acting fentanyl could be used for chronic non-cancer pain. There are disenrollment strategies outlined in the document for non-compliance to the REMS agreement but these have not been enforced.

Fentanyl and the opioid crisis

In the mid-2000s non-pharmaceutical Fentanyl began to appear in the United States from Toluca, Mexico which led to a surge of deaths in the Midwest. The laboratory manufacturing Fentanyl was seized in 2007 which stopped the deaths. The deaths were largely related to fentanyl adulerated heroin and cocaine (33,141). What became evident at the time was that fentanyl was more potent and deadly than heroin and could be transported easily since it weighed less than heroin and was more easily distributed. Fentanyl could be produced in laboratories without growing a crop in the open as is necessary for heroin. From 2000 through 2018 in Europe there has been a growing number of fentanyl deaths unrelated to pharmaceutical products. This is particularly true for Estonia where fentanyl analogues account for 70% of the fentanyl related deaths (114).

In the United States, while non-medical use of commercial opioids has stabilized or perhaps diminished in the past 5 years, the abuse of fentanyl and fentanyl analogues from non-pharmaceutical sources has skyrocketed and now account for 46% of opioid deaths from synthetic opioids (114). Fentanyl exposure is often initially unintentional but becomes the opioid of choice for a subset thereafter (142). Nearly 40% of individuals entering opioid addiction programs test positive for fentanyl (142). Individuals more likely to test positive for fentanyl have had recent opioid and cocaine use (142). Between 2012 and 2014 fentanyl-related deaths from non-pharmaceutical sources doubled and by 2015 fentanyl deaths exceeded heroin (143). Deaths attributable to fentanyl in 2016 were 9,945 but in the first 6 months of 2017 were 20,145 (144,145). Adding to the deaths are fentanyl adulterated alprazolam and oxycodone tablets from non-pharmaceutical sources (146-148).

Individuals misusing fentanyl underestimate or are unaware of fentanyl's potency and risk acute deaths for its euphoria. Non-pharmaceutical fentanyl products can be ordered on websites and darkweb sites. Products received often contain different amounts of fentanyl than what was ordered (149,150). The sites offer powders, pills, nasal preparations, patches, capsules, lozenges, liquids and blotting paper. Most sites originate from China and do business through Hong Kong. The usual price ranges between 2,000–4,000 dollars per kg of fentanyl (42). In 2011 there were 671 law enforcement seizures of non-pharmaceutical fentanyl substances but by a 2016 this had grown to 28,781. In 2011 there were no fentanyl analogues seizures but by 2016 there were 1,580 seizures of acetylfentanyl non-pharmaceutical preparations (143). There is likely an underestimation of fentanyl analogue deaths since most crime laboratories do not measure novel synthetic opioids, deaths may be attributed to heroin or cocaine in fentanyl analogue adulterated preparations. Fentanyl analogues are estimated to account for nearly 20% of fentanyl deaths (151).

Analogues are produced by replacing or substituting the propionyl chain or ethylphenyl moiety and adding or substituting a fluoro, chloro or methoxy group on the N-phenyl ring. The result is a greater affinity for the mu receptor (152-156). Carfentanil, the most notorious analogue, has a 10,000-fold greater affinity for the mu receptor than morphine, 2 μg can be fatal (157). As a result, very high doses of naloxone and/or continuous infusions are necessary to reverse respiratory depression (42,148,158).

Naloxone and fentanyl overdoses

Naloxone can be given intravenous, subcutaneous, intramuscular, intranasal, sublingual and by endotracheal inhalation. It has a rapid onset action which can be seen within 30 seconds given intravenous and within 2–5 minutes when given subcutaneous. It is also rapidly glucuronidated. The peak effect occurs at 30 minutes but has lost its effect by 90 minutes (159). The usual naloxone dose for heroin overdose is 400 mcg but is only effective in 15% of individuals with a fentanyl overdose (33). Naloxone infusions are frequently needed due to the rebound recirculation of fentanyl from fat and muscle

stores (160,161). It is recommended that patients not be discharged from the emergency department an hour after delivering naloxone as can frequently be done with heroin overdoses (162). The use of naloxone take home kits have been reported from Canada. Most overdoses requiring home-based naloxone occurred among males (60.2%) and in a private residence (72.0%). Fentanyl and carfentanil were the most common substances reported during overdose events (163). The mean dose to reverse fentanyl respiratory depression is 3.36 mg and with fentanyl analogues as high as 10–20 mg (33,95,164,165). Enzyme-linked immunoassays developed for fentanyl cannot separate fentanyl from more potent analogues such that doses of naloxone depend on clinical responses rather than on the type of analogue (166). Carfentanil is the deadliest fentanyl analogue and may require up to 100 mg of naloxone to reverse respiratory depression (167-169).

There are several naloxone dosing strategies reported. First responders should give 2 mg of naloxone intranasal twice at short intervals (57). In the emergency department, 0.4 mg by rapid IV push is followed by 0.8 mg IV at 1–2 minutes intervals (157,170,171). The lack of response to low doses of naloxone should not deter clinicians from repeating doses while waiting for a drug screen.

Conclusions

Fentanyl has a unique pharmacology which reduces it utility as an analgesic relative to other opioids. Fentanyl transdermal patches are easily tampered and contain lethal doses of fentanyl even after 3 days of use. A single diverted 50 mcg patch can be fatal to an opioid naive individual. Rapid-acting fentanyl for cancer breakthrough pain in opioid tolerant individuals has a marginal clinical benefit and is very costly. It should be used as a last resort for breakthrough pain. Fentanyl abuse and deaths have become the major concern in the opioid crisis. The lethality of fentanyl analogues is well illustrated by mortality figures and emergency department experiences.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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