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Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review

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Keywords: opioid, synthetic opioids, fentanyl, fentanyl analog, carfentanil, naloxone

Abbreviations:

4-ANPP: 4-anilino-N-phenethyl-4-piperidine; ANPP

4Cl-iBF: 4-chloroisobutyrylfentanyl

4F-iBF: 4-fluoroisobutyrylfentanyl

AEI: Advanced electronic information

AMF: alpha-methylfentanyl

CBP: US Customs and Border Protection

CDC: Centers for Disease Control

CDSA: Controlled Drug and Substance Act (Canada)

CNS: central nervous system

DEA: US Drug Enforcement Agency

DTO: Drug trafficking organization

ED: Emergency department

ELISA: enzyme-linked immunosorbent assay

EMCDDA: European Monitoring Centre for Drug and Drug Addiction

FDA: US Food and Drug Administration

GC-MS: gas chromatography mass spectrometry

ICU: intensive care unit

IN: intranasal

IV: intravenous

LC-HRMS: liquid chromatography high resolution mass spectrometry

LC-MS/MS: liquid chromatography tandem mass spectrometry

MDA: United Kingdom Misuse of Drugs Act

NPF: non-pharmaceutical fentanyl

THF-F: tetrahydrofuranfentanyl

US: United States

USPS: US Postal Service

UNODC: United Nations office on drugs and crime

1. Introduction

The death rate due to opioid analgesics nearly quadrupled in the US from 1999 to 2011 and was responsible for 33,091 deaths in 2015 (CDC, 2014; Rudd et al., 2016). The increased demand for opioids has led to the increased availability of heroin and the proliferation of real and counterfeit opioid pills in the illicit drug market. Synthetic opioids such as fentanyl, fentanyl analogs, and other novel compounds such as U-47700 and MT-45 are an emerging public health threat, detected in white heroin, black tar heroin, and pills. Although some are banned by the US DEA and international drug agencies, clandestine

manufacturers are able to produce drug analogs at a faster rate than these compounds can be controlled, or scheduled, a process that requires lengthy evidence gathering by drug agencies. Detection requires specialized testing and clinicians need to have a strong index of suspicion to recognize the possibility of a synthetic opioid causing respiratory depression, altered mental status, miosis, and the other hallmarks of opioid toxicity in patients. In this review, we discuss the multifactorial aspects of fentanyl, fentanyl analog, and novel synthetic opioids in regards to epidemiology, legal status, pharmacology, detection, and care of the poisoned patient.

2. Methods

2.1 Search Strategy

A systematic search for articles about synthetic opioids, including fentanyl, fentanyl analogues, and other novel psychoactive substances, was conducted in PubMed on May 1, 2017. A broad search technique was used in order to encompass all subject areas detailed in this review, and irrelevant articles were excluded from the results. Preliminary searching in Embase and Google Scholar did not yield additional unique results; therefore, the search was limited to PubMed. Cited reference searching and grey literature searching in Google were used to identify additional articles and government reports. To gain current information about trafficking and legal status, which were less likely to be found in scholarly journals, Google was searched for governmental documents pertinent to the topic. Google searches were also performed for websites selling

drugs and drug production equipment. Detailed search strategies can be found in Appendix 1.

2.2 Study Selection

The literature search returned 404 articles from PubMed (Figure 1). An additional 31 reports and news articles were found in Google and deemed to be relevant. These were evaluated independently of the journal articles. 404 articles were screened for inclusion, and 132 were eliminated because of their irrelevance to the topic. The full text of 268 journal articles were screened for eligibility, and 161 were excluded in final screening, due to repetition of information. 142 journal articles from the original search strategy were used in the final analysis.

3. Current state of synthetic opioids

3.1 Epidemiology and Legal Status

3.1.1 Fentanyl

Fentanyl was first synthesized in 1960 by Paul Janssen in Belgium and marketed as a medicine for treating pain (Figure 2). It was approved by the US FDA as an intravenous anesthetic in 1972, marketed under the trade name Sublimaze®. Within a year of going off patent (1981), sales of fentanyl increased 10-fold (Stanley, 2014). Reports of misuse and illicit use by clinicians, primarily anesthesiologists and surgeons with access to the drug, were first reported in the 1980s and continued into the early 2000s (Ward et al., 1983; Garriott et al., 1984; Silsby et al., 1984; Rosenberg, 1986; Pare et al., 1987; Kintz et al., 2005; Bryson

and Silverstein, 2008; Jugerman et al., 2012). In the 1990s fentanyl transdermal patches were introduced for widespread palliative use and access extended from clinicians to include patients. As a result, reports of overdoses caused by the misuse of fentanyl transdermal patches emerged in the 1990s and continued into the early 2000s (Rose et al., 1993; Marquardt and Tharratt, 1994; Flannagan et al., 1996; Edinboro et al., 1997; Kramer and Tawney, 1998; Frolich et al., 2001; Reeves and Ginifer, 2002; Tharp et al., 2004; Coon et al., 2005; Teske et al., 2007). In 1994, the FDA issued a warning regarding the dangers associated with fentanyl patches, expressing that it should only be prescribed to those with severe pain that cannot be managed by less potent opioids (Wyman, 1994).

A significant rise in overdose deaths from illicitly manufactured nonpharmaceutical fentanyl (NPF) occurred in the mid-2000s. In May 2006, the CDC and DEA implemented a surveillance system, which identified 1,013 NPF-related deaths that occurred from April 4, 2005 to March 28, 2007 (Jones et al., 2008). Most of the implicated NPF originated from adulterated heroin or cocaine that was sold as a street drug and injected. The largest number of deaths occurred in metropolitan Chicago, Detroit, and Philadelphia, however, other NPF related deaths were also reported in suburban and rural areas in Midwestern and Eastern states (Jones et al., 2008). DEA officials traced the trail of deadly NPF to a single clandestine laboratory in Toluca, Mexico. The seizure of this laboratory and the DEA scheduling of the fentanyl precursors brought an end to this outbreak in 2007.

The mid 2010s marked the rise in counterfeit pills containing NPF and a re-emergence of NPF-laced heroin and cocaine. From 2012 to 2014, the number of reported NPF related deaths in the US more than doubled (Gladden et al., 2016). In 2014, counterfeit prescription pills containing fentanyl were seized for the first time in the US (DEA, 2016). This rise in NPF has created a significant public health crisis since those exposed are unaware of the adulteration, but rather assume they were using standard heroin, cocaine, or prescription strength opioid pills. Street-purchased counterfeit Xanax and Norco pills containing fentanyl were responsible for two overdose outbreaks in northern California from late 2015-2016 (Arens et al., 2016; Vo et al., 2016; Sutter et al., 2016). NPF-adulteration is not limited to heroin and other illicitly produced opioid analgesics, but has also been found in cocaine. This poses a significant risk given that many cocaine users may be opioid naïve and thus have more significant clinical outcomes. Thirteen fentanyl overdoses were reported in June 2016 in Connecticut related to fentanyl-adulterated cocaine (Tomassoni et al., 2017). Nine patients were admitted to the hospital, including four to the ICU. Three required endotracheal intubation and three patients died. The rise in the production of counterfeit pills and NPF-laced heroin and cocaine is expected to continue due to the ease of manufacturing and readily available precursors shipped from China (see section 3.2).

3.1.2 Fentanyl analogs

Following the synthesis of fentanyl in 1960, many fentanyl analogs were developed for medicinal and veterinary use including sufentanil, alfentanil,

remifentanil, and carfentanil. To date no reports of misuse of these pharmaceutical analogs (besides carfentanil, see below) have been reported. The DEA has classified fentanyl analogs that are prescription analgesics or veterinary medicines as Schedule II Narcotics.

Starting in the winter of 1979 multiple opioid overdoses were identified in California from the use of “China White” or synthetic heroin, but no heroin or other known opioids were detected by toxicology analysis. The causative agent was eventually identified to be alpha-methylfentanyl (AMF) (Kram et al., 1981; Henderson, 1988; Henderson, 1991). Another analog, 3-methylfentanyl, emerged in 1984 in Allegheny County, Pennsylvania and was responsible for 16 fatal overdose cases (Hibbs et al., 1991). Alpha-methyl and methylfentanyl were subsequently classified as schedule I narcotics in 1981 and 1986 respectively. Following the emergence of these two analogs, the Federal Analogue Act, a section of the US Controlled Substances Act, passed in 1986. This act allows any chemical “substantially similar” to a controlled substance listed in Schedule I or II to be treated as if it were also listed in those schedules, but only if intended for human consumption. This act has proven difficult to enforce in specific cases tried in the US judicial system due to the need to prove that a defined substance is indeed “substantially similar” and was intended for human consumption (United States v. Forbes, 1992; United States v. Roberts, 2002; United States v. Brown, 2003).

In the mid to late 1980s at least ten additional analogs were identified on the black market and reported to be responsible for overdoses related to NPF-

laced heroin (Henderson, 1991). In California alone, fentanyl analogs were determined to be responsible for >100 overdose deaths from 1979-1991 (Henderson, 1991). In response, these additional fentanyl analogs were added as schedule I narcotics (Table 1).

In 2013, acetylfentanyl emerged as yet another fentanyl analog responsible for numerous fatalities in Rhode Island, Pennsylvania, and North Carolina (Lozier et al., 2015; Rogers et al., 2015). It is believed that the magnitude of this outbreak is underappreciated since acetylfentanyl is not routinely monitored by clinical and forensic toxicology laboratories. The CDC published a public health advisory in 2015 recommending more expansive toxicological analysis when sudden increases in opioid overdoses occur (CDC, 2015). In 2015, the DEA announced the scheduling of acetylfentanyl as a Schedule I narcotic.

In 2016, the DEA declared that butyryl fentanyl and beta-hydroxythiofentanyl were associated with numerous fatalities in 2015 and classified them as Schedule I narcotics. At least 40 confirmed overdose deaths involving butyryl fentanyl abuse were reported in Maryland (1), New York (38), and Oregon (1) and at least seven confirmed overdose fatalities involving beta-hydroxythiofentanyl were reported in Florida (DEA, 2016). Cases from 2015 involving butyryl fentanyl were also published in the scientific literature (Cole et al., 2015; McIntyre, et al., 2016; Staeheli et. al., 2016; Poklis, et al., 2016), however, no cases involving beta-hydroxythiofentanyl have been reported to date. Carfentanil, synthesized by Janseen Pharmaceutica in 1974 and used as a

general anesthetic for large animals, has also made its way into the heroin supply in the US. The first outbreak occurred in the Midwest and Appalachian region in August-September 2016. The DEA estimated 300 carfentanil overdoses during this time.

The legal status of fentanyl analogs in the US and the European Union has largely been reactive rather than proactive. The Commission on Narcotic Drugs within the United Nations Office on Drug and Crime (UNODC) was created in 1946 to assist in supervising the application of the international drug control treaties. The Single Convention on Narcotic Drugs (1961) is an international treaty aimed to combat drug abuse by coordinated international actions. Through this treaty greater than 77 synthetic opioids are classified as Schedule I. Since the Single Convention is not self-executing, parties must pass laws to carry out its provisions, and the UNODC works with countries' legislatures to ensure compliance. Acetylfentanyl is the most recent (2016) synthetic opioid classified as Schedule I under the Single Convention on Narcotic Drugs Treaty. In some cases, scheduling in member states precedes UN scheduling and in other cases the member states schedule drugs in response to rulings by the Commission on Narcotic Drugs. Scheduling of narcotic drugs under international rule is listed for drugs included in Table 1. The European Monitoring Centre for Drug and Drug Addiction (EMCDDA) for the European Union primarily classifies drugs and precursors according to the UN Conventions and Treaties. In addition, many countries have Acts similar to the US Federal Analogue Act. In Canada, the Controlled Drug and Substance Act (CDSA) of 1996 classified "fentanyls, their

salts, derivatives and analogs and salts of derivatives and analogs” as Schedule I drugs. Similarly, the UK Misuse of Drugs Act (MDA) was amended in 1987 to classify any compound structurally derived from fentanyl by medication (replacement, substitution) as part I Class A drugs.

The STRIDA project, which monitors the occurrence and health hazards of novel psychoactive substances in Sweden, has reported the detection of numerous fentanyl analogs (2015-2017) including furanylfentanyl, 4-fluorobutyrylfentanyl, 4-methoxybutyrylfentanyl, acrylfentanyl, 4-chloroisobutyrylfentanyl (4Cl-iBF), 4-fluoroisobutyrylfentanyl (4F-iBF), tetrahydrofuranfentanyl (THF-F), and cyclopentylfentanyl, however, these have yet to be seen in abundance in the US (Bäckberg et al., 2015; Helander et al., 2016; Helander et al., 2016). The STRIDA project is an excellent case study for how drug regulations can drive the market. As the number of intoxications and fatalities related to fentanyl analogs started to increase in 2014/2015, butyrylfentanyl and acetylfentanyl became classified as narcotic substances and 4-fluorobutyrylfentanyl as harmful to health in 2015 in Sweden. Once banned, the analogs disappeared from online markets and were replaced by two unclassified variants, 4-methoxybutyrylfentanyl and furanylfentanyl, which in turn were classified in 2016. Acrylfentanyl then immediately appeared in online markets as an alternative and cases of medical complications involving acrylfentanyl were reported within a couple of months (Helander, A., 2017). Acrylfentanyl became regulated as a narcotic in Sweden in August 2016 and yet again new fentanyl analogs (4F-iBF, 4Cl-iBF, THF-F, CP-F, valerylfentanyl, and

methoxyacetylfentanyl) emerged. These analogs were regulated in January 2017.

3.1.3 Novel Synthetic Opioids

In addition to fentanyl analogs, AH-7921, U-47700, and MT-45 have emerged as novel synthetic opioids. These synthetic opioids have not been identified as contaminants in the heroin supply, but rather are purchased directly for use as reported by users from published case reports. No systematic studies have been conducted to fully understand how these novel synthetic opioids are obtained and distributed, however, they are readily available via the internet. AH-7921 and U-47700 are structural isomers synthesized in the 1970s by Allen and Hanburys Ltd (“AH” synthetic opioids) and Upjohn Pharmaceutical (“U” synthetic opioids), respectively. There is no systematic naming process for these synthetic opioids. Development was abandoned due to their addictive properties. In 2013, AH-7921 was discovered as an active ingredient in synthetic cannabis products in Japan (Uchiyama et al., 2013). It has since been identified in numerous overdose cases across Europe and the US (Vorce et al., 2014; Karinen et al., 2014; Coppola and Mondola, 2014; Katselou et al., 2015; Fels et al., 2017). Similarly, the DEA received reports of at least 46 confirmed fatalities in 2015/2016 resulting from the use of U-47700. Numerous overdose reports have also surfaced in the scientific literature starting in 2016 (Elliott et al., 2016; Coopman et al., 2016; Ruan et al., 2016; Domanski et al., 2017; Schneir et al., 2017; Armenian et al., 2017; Jones et al., 2017; Mohr et al., 2016; Vo et al., 2017; McIntyre et al., 2017; Dziadosz et al., 2017). MT-45 was first reported as an NPS

through the Early Warning System of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in December 2013. Since that time reports of abuse and overdose have been reported in Europe and the US (Helander et al., 2014; Papsun et al., 2016; Helander et al., 2017; Fels et al., 2017).

3.2 Trafficking

The present fentanyl epidemic, which began in 2013, marks a shift in trafficking and sales that does not appear to be abating, and is not an isolated incident like prior fentanyl outbreaks (DEA Intelligence Brief, 2016). Several factors have contributed to the proliferation of fentanyl, fentanyl analogs, and novel synthetic opioids in the illicit drug market. These include ease of availability, profitability, and increasing restrictions on prescription opioids with a large opioid-abusing population.

Modern internet e-commerce has enabled individual players, small-scale drug trafficking organizations (DTOs) and large-scale DTOs with their own production facilities to flood the illicit drug market with fentanyl (DEA Intelligence Brief, 2016). Fentanyl, fentanyl precursors, fentanyl analogs, novel synthetic opioids and other 'research chemicals' can be bought in multiple kilogram quantities from online vendors, both using conventional internet (surface web) and on the dark web (darknet) using common modes of payment such as credit cards, Western Union, PayPal, Moneygram, bank transfers, and cryptocurrencies such as Bitcoin (Armenian et al., 2015). Dark web content is not indexed by search engines and requires specific software or browsers to access, such as onion routing for the Tor network. Because of the high level of encryption, illegal

drug transactions using encrypted currencies can be performed. However, the surface web may be a more common source for these drugs. For example, a recent search yielded a webstore operating out of Hong Kong, with production facilities in China, selling 90 different synthetic opioids, of which 9 were U-compounds (such as U-47700), 23 were fentanyl compounds including a fentanyl precursor (4-anilino-N-phenethyl-4-piperidine: abbr. 4-ANPP) and 3 carfentanil analogs (sufentanil, lofentanil, 3-carbomethoxyfentanyl) (Drugs Power Store, 2017). Wholesale prices range from about \$2000-4000 per kg of fentanyl or fentanyl analog (DEA Intelligence Brief, 2016).

Surface websites are not only selling the drugs, but also tools for pill manufacturing, such as pill presses and pill die molds. Although pill presses are regulated by the DEA, vendors are able to ship them to the US unassembled and in multiple packages, thus evading detection by Customs and Border Protection officials (DEA Intelligence Brief, 2016). Pill die molds for brand name Norco and Xanax, and generic oxycodone, oxymorphone, acetaminophen/hydrocodone, acetaminophen/oxycodone, and other prescription drugs are readily found on online auction websites such as Ebay and online marketplaces (dhgate.com, alibaba.com, aliexpress.com, punchdies.com). A recent Ebay search yielded 17 results for Watson 853 pill die molds (Norco) and 13 results for R039 pill die molds (Xanax) ranging in price from \$65-\$189 (Ebay, 2017). Considering that opioid pill street value ranges from \$10-20 per pill, 1 kg fentanyl can translate into \$5-20 million in retail sales, making illicit fentanyl sales very profitable and

accessible to individual drug dealers as well as large scale DTOs (DEA Intelligence Brief, 2016).

Synthetic opioids primarily enter the US and Canada through China (DEA, 2016; Senate Resolution 10, 2017). Many clandestine and legitimate laboratories are supply sources in China, where the chemical and pharmaceutical industries are weakly regulated and poorly monitored (O'Connor, S. 2017). International shipments enter the US by freight forwarders, US Postal Service (USPS), and express consignment couriers (i.e. UPS, FedEx, DHL) and may or may not have advanced electronic information (AEI) reported. In a recent Senate subcommittee hearing, officials from the USPS and CBP remarked on the large amount of international mail that doesn't have AEI, which means the processing of these items is largely manual (Stopping Shipment of Synthetic Opioids, 2017). A substantial amount of synthetic opioids and fentanyl precursors are first sent to Mexico, and a minor proportion to Canada. In Canada, they will then enter the local drug markets with some diverted to the US for sale in primarily Northeastern drug markets. In Mexico, large-scale DTOs including the Mexican cartels synthesize fentanyl from precursors, manufacture illicit opioid pills, and cut both white and black tar heroin with fentanyl. From there, the drugs enter the US through the southwestern border, the USPS or express consignment couriers. Mexican drug cartels are the primary channel for Chinese fentanyl destined for the US and are directly responsible for the increased availability of heroin in the US (O'Connor, S. 2017; Senate Resolution 10, 2017). A US Senate resolution from Jan 10, 2017 discussed fentanyl and fentanyl analog trafficking into the US

from China and Mexico, resolving that close cooperation between the governments of all three countries is needed to help stop its' production and trafficking (Senate Resolution 10, 2017). In order to curb the mailing of drugs through the USPS, the STOP Act of 2017 has been introduced to the US Senate and is currently referred to the Committee on Finance (S. 372, 2017). It would require the USPS to have advanced electronic information on all inbound international parcels available to the U.S. Customs and Border Protection (S. 372, 2017). Although more of a widespread problem in North America, fentanyl and fentanyl analog outbreaks have also been reported in Europe, Japan, and Brazil (UNODC, 2017).

4. Clinical pharmacology of synthetic opioids

4.1 Metabolism

4.1.1 Fentanyl

Fentanyl is eliminated through biotransformation by the liver (CYP 3A4) into norfentanyl and through oxidative N-dealkylation at the piperidine ring (Tateishi et al., 1996). Minor metabolites are also created through various other pathways. For example, despropionylfentanyl is formed by carboxamide hydrolysis, while both hydroxyfentanyl and hydroxynorfentanyl metabolites are hydroxylated at the propionyl moiety (Watanabe et al., 2017). All metabolites are inactive, and only a small amount of fentanyl (8-10%) is renally and fecally cleared (McClain & Hug, 1980; Mather, 1983; Poklis, 1995).

4.1.2 Fentanyl analogs

Like fentanyl, analogs such as alpha-methylfentanyl, alfentanil, butyrfentanyl, carfentanil, and sufentanil are primarily metabolized via the CYP 3A4 hepatic pathway, generating N-dealkylated metabolites that are primarily inactive (Guitton et al., 1997; Sato et al., 2010, Feasel et al., 2016). An important point to note is that sufentanil and alfentanil are metabolized into the same N-dealkylated product, making forensic distinction impossible when only this metabolite is identified (Guitton et al., 1997). Carfentanil has 12 metabolites and while phase I biotransformations dominate metabolite formation, the N-dealkylated norcarfentanil is not the only abundant metabolite. The other is formed after monohydroxylation at the piperidine ring (Feasel et al., 2016). An in vivo evaluation of butyrfentanyl in a post-mortem case revealed hydroxylation of the butanamide side chain followed by subsequent oxidation to the carboxylic acid, representing the major metabolic step (Steuer et al., 2016). Hydroxybutyrfentanyl is also a major metabolite (Staehele et al., 2016). CYP3A4 and CYP2D6 are implicated in butyrfentanyl metabolism.

Like fentanyl and other fentanyl analogs, acetylfentanyl, acrylfentanyl, and 4-fluoro-isobutyrfentanyl each have a major inactive nor-metabolite produced by N-dealkylation (Watanabe et al., 2017). In addition, each also has a hydroxyethyl and hydroxymethoxy metabolite, similar to fentanyl. Other metabolites are formed via various pathways including, but not limited to, glucuronidation, sulfation, dihydroxylation, monohydroxylation, carbonylation, and dihydrodiol formation. Acetylfentanyl was found to have 32, acrylfentanyl 14, and 4-fluoro-isobutyrfentanyl 17 metabolites.

Furanylfentanyl has 14 metabolites, but its major metabolite is not produced by N-dealkylation. Instead, it undergoes amide hydrolysis to produce an intact phenethylpiperidine moiety, which could be further metabolized. Another study of a set of presumptive heroin-positive urine specimens demonstrated a dihydrodiol metabolite and fentanyl precursor, 4-ANPP, and a sulfate metabolite (Goggin et al., 2017). The difference in the metabolism of furanylfentanyl is attributed to its structure; while acetylfentanyl, acrylfentanyl, 4-fluoro-isobutylylfentanyl contain a different substituent at the amide group, furan is an aromatic, heterocyclic system known to undergo characteristic reactions (Watanabe et al., 2017)

Remifentanil is the only analog found to be 95% metabolized in the blood and tissues by non-CYP enzymes (Burkle et al., 1996). This is attributed to an easily accessible ester group allowing for rapid hydrolysis by circulating blood esterases. The N-dealkylated metabolite is minor, but shares the same structure as carfentanil's nor- metabolite, making laboratory distinction difficult (Feasel et al., 2016).

4.1.3 Novel synthetic opioids

Little is known regarding the metabolism of novel synthetic opioids. Demethylation is the predominant mechanism in the metabolism of AH-7921, which has 12 identified metabolites (Wohlfarth et al., 2015). Jones et al. described an overdose case with insufflation and injection of U-47700 and identified N-desmethyl, N,N-didesmethyl, desmethylhydroxy, and N,N-

didesmethylhydroxy metabolites in urine (Jones et al., 2016). Fleming et al. detected the same metabolites in 4 cases of U-47700 (Fleming et al., 2017).

4.2 Pharmacokinetics and pharmacodynamics

4.2.1 Fentanyl & fentanyl analogs

Fentanyl and fentanyl analogs are full agonists at the μ -opioid receptor and potencies of these medications, typically in relation to morphine, are described throughout the medical literature. However, sound evidence supporting statements of potency are lacking. Early studies evaluating pharmacokinetics and pharmacodynamics of synthetic opioids were performed in rat or guinea pig models. Onset, potency, and duration of analgesic action were assessed via a rat tail withdrawal test after administration of the synthetic opioid, in which analgesic sufficiency is measured by latency of removal from stimuli after the rat's tail is submerged in a hot water bath (Janssen, 1963; Van Bever et al., 1976). In those studies, potency was also described in terms of mean effective dose and lethal dose. Measured values from in vivo studies are commonly compared to those from in vitro guinea pig ileum assays which, historically, have been the gold-standard for μ -opioid receptor pharmacology (Hayes et al., 1985; Feasel 2016). In addition, early human studies describing the relative potency of fentanyl to morphine evaluated a small cohort of patients after narcotic-supplemented general anesthesia and their first postoperative request for pain relief (Romagnoli, 1973; Keeri-Szanto, 1974). Therefore, while robust data is lacking in regards to statements regarding fentanyl's potency being approximately 50-100

times the potency of morphine or carfentanil's potency being 10,000 times that of morphine, for example, such early dose-response studies can be helpful in quantifying therapeutic effects of opioid analgesics. The relation to clinical poisoning and human risk assessment, however, is more difficult to determine. Nevertheless, the potencies of various analogs have been described in the literature: acetylfentanyl (also known as desmethylyfentanyl) is 5-15 times more potent than heroin (Yonemitsu 2016) with an ED50 and LD50 ten times narrower than that of morphine (Takase et al., 2016), butyrfentanyl is 7 times more potent than morphine (Steuer et al., 2016), carfentanil has the lowest ED50 of the analogs (Subramanian et al., 2000), and ocfentanil (also called A-3217) is approximately 90 times as potent as morphine (Fletcher et al., 1991).

Other pharmacokinetic properties of fentanyl are better known. The high lipophilicity of fentanyl and its analogs enables rapid diffusion through membranes, including the blood brain barrier. Fentanyl is quickly taken up into tissues, leading to an initial fall in plasma levels within 60 minutes (McClain & Hug, 1980). The elimination half-life of fentanyl is approximately 219 minutes, accounting for its slow redistribution into the central compartment, and responsible for prolonged clinical effects (McClain & Hug, 1980).

When used transdermally, fentanyl is continually absorbed for up to 12 hours after removal of the patch, due to a depot of drug that forms on the skin (Nelson & Schwaner, 2009; Oliveira et al., 2012). A very small amount (2-3%) can be present on the skin 48 hours after application (Oliveira et al., 2012). Intranasal administration of fentanyl has a bioavailability of 89% and reaches

maximum serum concentration in a matter of minutes, with effects lasting about 1-2 hours (Christrup et al., 2008). Oral transmucosal administration has the least bioavailability (50%), the shortest time to onset of effects (5 minutes), and a duration of action of 2-3 hours (Streisaand et al., 1991).

Data regarding pharmacokinetic and pharmacodynamic properties of fentanyl analogues in humans is scarce and much of the data that exists is in animal models. High lipophilicity, ease of crossing the blood brain barrier, and high receptor affinity are reasons for increased potency. High selectivity and specificity for the μ -opioid receptor over other opioid receptor subtypes also contribute to its clinical effects (Maguire et al., 1992).

4.2.2 Novel synthetic opioids

Novel synthetic opioids have not been studied in humans and therefore, pharmacokinetic data does not exist. However, for an agent such as U-47700, typical opioid pharmacology is expected as seen in animal models and as demonstrated in various case studies (Fleming et al., 2017). Such models revealed that U-47700 is 7.5 times more potent in binding to opioid receptors than morphine (Harper et al., 1974). In general, novel synthetic opioids are highly selective for the μ -receptor. The molecule by which U-47700 was derived, AH-7921, is thought to have approximately the same potency as morphine (Hayes & Tyers, 1983).

5. Analytical detection

The true extent of the synthetic opioid epidemic is underappreciated due to the lack of routine diagnostic monitoring. Standard immunoassay screening in the clinical setting does not detect synthetic opioids. FDA approved opiate immunoassays included in routine urine toxicology testing do not cross-react with the synthetic opioids since they have little structural homology to morphine. More complex methods such as gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) are required for definitive detection. In the early 2010s, the need for fentanyl compliance monitoring for chronic pain management patients led to the development of automated fentanyl immunoassays. However, to this date a limited number have been validated for clinical use. Additionally, very few clinical laboratories offer fentanyl testing in real time.

The development of the first automated homogeneous enzyme immunoassay for the detection of fentanyl in urine was published in 2011 (Immunoanalysis Corporation) (Wang et al., 2011). This assay cross-reacts with two major fentanyl metabolites, hydroxyfentanyl and depropionylfentanyl, but fails to detect norfentanyl. An independent laboratory evaluation of this assay demonstrated it to be rapid and accurate (99%) for fentanyl detection in monitoring fentanyl compliance and abuse (Synder et al., 2011). The manufacturer claims that the assay cross-reacts (>10% cross-reactivity) with 4-methylbutyryl fentanyl, acetyl fentanyl, butyrylfentanyl, carfentanil, furanylfentanyl, isobutyrylfentanyl, trans-methylfentanyl, and valerylfentanyl, however, this has not been independently confirmed. A similar automated homogeneous enzyme

immunoassay (DRI® Fentanyl Assay, Thermo Scientific) was proven to cross-react with acetylfentanyl (Wang et al., 2014). However, risperidone and 9-hydroxyrisperidone were also found to cross-react, whereas norfentanyl did not. Fentanyl, acetylfentanyl, risperidone, and 9-hydroxyrisperidone all share an intramolecular alkylated piperidine (3-methyl-5-piperidino-2-pentene) that is not present in norfentanyl. This is likely recognized in part by the antibody for the immunoassay. The presence of this moiety could potentially be used to predict cross-reactivity with other fentanyl analogs, however, detection of these compounds has not been analytically evaluated for this assay.

Specific enzyme-linked immunosorbent assays (ELISAs) are also available for fentanyl, MT-45, AH-7921, and U-47700 (Randox Toxicology), but are more manual processes compared to automated immunoassays. Randox Toxicology also offers an automated designer fentanyl and opioids biochip array that detects fentanyl and 12 additional synthetic opioids, however, this assay has not been independently evaluated. The fentanyl immunoassays and ELISAs can be used to screen for fentanyl and select fentanyl analogs; however, confirmatory testing by mass spectrometry is required for all samples that screen positive to determine the exact drug responsible for the positive screen.

Prior to the introduction of automated immunoassays, clinical and forensic laboratories primarily relied upon mass spectrometric methods for the detection of fentanyl, fentanyl analogs, and other synthetic opioids. Numerous methods have been published dating back to the early 1980s. Mass spectrometry is still required for definitive detection, but is often not routinely available in hospital

laboratories for real time testing. GC-MS has the advantage of offering untargeted data acquisition with library searching of acquired mass spectra for compounds detected in biological specimens. Large GC-MS mass spectral libraries are commercially available and transferrable across different vendors' instruments. In recent years, considerable focus has been devoted to adding designer drug and novel psychoactive substance spectra to commercial libraries. However, GC-MS methods are not capable of directly analyzing drugs that are nonvolatile, polar, or thermally labile. Thus lengthy sample preparation techniques are required and are not amenable to routine rapid testing in biological samples. Although this requirement isn't necessary for LC-MS/MS methods, these methods are commonly targeted and will only detect compounds for which the method was designed. Targeted LC-MS/MS methods designed to simultaneously detect fentanyl, fentanyl analogs, and other synthetic opioids were first published in 2009 (Lurie and Iio, 2009; Gergov et al., 2009) and variations of these methods are still used in laboratories. LC-MS/MS has also been used to profile illicit fentanyl in seized drugs by targeting 40 fentanyl processing impurities significant for a specific synthetic route (Lurie et al., 2012).

Given the continued emergence of novel synthetics, the major disadvantage of GC-MS and LC-MS/MS is that the methods are often targeted in nature or limited by the availability of pre-established mass spectral libraries. Additionally, results are seldom available rapidly enough to contribute to the immediate care of a patient or the real-time detection of an outbreak. Liquid chromatography high resolution mass spectrometry (LC-HRMS) using

quadrupole time-of-flight or orbitrap technology offers potential advantages in clinical toxicology (Wu et al., 2012). Tentative identification of unknowns can be made without the availability of a reference standard or a library spectrum. Data is acquired in an untargeted manner and can be retrospectively analyzed for new and emerging synthetics. In recent years, LC-HRMS has been used for the detection of synthetic opioids such as butyrfentanyl, 4-fluorobutyrfentanyl, acetylfentanyl, 4-methoxybutyrfentanyl, furanylfentanyl, acrylfentanyl, 4Cl-iBF, 4F-iBF, THF-F, cyclopentylfentanyl, AH-7921, MT-45, and U-47700 in individual cases, case series, outbreaks, and epidemiological surveillance efforts (Backberg et al., 2015; Wohlfarth et al., 2016; Helander et al., 2016; Schneir et al., 2017; Armenian et al., 2017; Breindahl et al., 2017; Jones et al., 2017; Steuer et al., 2016; Vo et al., 2017; Fleming et al., 2017; Guerrieri et al., 2017; Helander et al., 2017; Goggin et al., 2017; Watanabe et al., 2017; Fels et al., 2017). It has also been used for the elucidation of the metabolic pathways of emerging synthetic opioids, such as, AH-7921, butyrfentanyl, carfentanil, U-47700, furanylfentanyl, acetylfentanyl, acrylfentanyl, and 4F-iBF (Wohlfarth et al., 2016; Jones et al., 2017; Steuer et al., 2016; Feasel et al., 2016; Fleming et al., 2017; Goggin et al., 2017; Watanabe et al., 2017). LC-HRMS has clearly emerged as the predominant method for the detection of novel synthetic opioids, however, this technology is not readily available in most routine clinical and forensic laboratories.

Point-of-care testing strips are available for rapid testing of urine with varying degrees of accuracy. There has been recent interest in the use of these

strips for point-of-use testing to detect the presence of fentanyl and analogs in drug products prior to use. This and potentially other pill testing technologies could be provided at safe injection facilities, needle exchanges, and festivals to detect the presence of fentanyl. More research is needed to determine the accuracy of these strips and their cross-reactivity with fentanyl analogs. It is yet to be determined if these strips could lead to significant harm reduction among users and how knowledge of the presence of synthetic opioids would alter patterns of use.

6. Care of the poisoned patient

6.1 Clinical Effects

6.1.1 Fentanyl

Fentanyl has a high affinity for μ -opioid receptors, which accounts for the profound central nervous system and respiratory depression responsible for its significant morbidity and mortality. Clinical effects are dose dependent, ranging from serum concentrations of 0.3-0.7 ng/ml providing analgesia alone to >3 ng/ml causing loss of protective airway reflexes and CNS depression in opioid naïve patients (Kumar et al., 1987, Nelson and Schwaner, 2009). Intubation and prolonged ICU courses have been described (Tomassoni et al., 2017). Deaths have been reported in a range of patient settings with post-mortem serum concentrations ranging from 3-383ng/ml (Martin et al., 2006). These levels, however, offer little insight into clinical management of a fentanyl-poisoned

patient as cases vary widely in terms of patient demographics, amount used, method of use, and coingestions.

Similar to other opioid agonists, fentanyl's effects include analgesia, anxiolysis, euphoria, drowsiness, and feelings of relaxation (Suzuki and El-Haddad, 2017). Undesired consequences include constipation, nausea, pruritus, cough suppression, orthostatic hypotension, urinary urgency or retention, and chest wall rigidity, particularly with IV usage. Respiratory depression is maximal 25 minutes after a single IV dose and can last as long as 2-3 hours (Harper et al., 1976, McClain and Hug, 1980).

Atypical overdose characteristics have also been reported after usage of fentanyl and fentanyl analogs. In a retrospective study regarding opioid deaths in Massachusetts from 2012-2014, uncommon symptoms included immediate blue discoloration of the lips (20%), gurgling sounds with breathing (16%), stiffening of the body or seizure-like activity (13%), foaming at the mouth (6%), and confusion or strange affect before unresponsiveness (6%) (Somerville et al., 2017). In addition, chest wall rigidity is thought to be a cause of rapid death after fentanyl usage (Burns et al., 2016)

Rare adverse effects after fentanyl usage include diffuse alveolar hemorrhage immediately after insufflating fentanyl powder in a 45 year old male who developed hypoxic respiratory failure (Ruzycki et al., 2016). Toxic leukoencephalopathy characterized by cerebellar white matter changes on T2-weighted MRI was an atypical finding in a 19 month old girl found unresponsive after inadvertent placement of a fentanyl transdermal patch on her back (Foy et

al., 2011). A 32 year old woman presented to the emergency department with syncope and chest pain mimicking acute coronary syndrome after using three fentanyl transdermal patches to alleviate knee pain, and developed non-specific T-wave changes on electrocardiogram (Kucuk et al., 2016).

6.1.2 Fentanyl analogs

Because fentanyl analogs share a similar mechanism of action to fentanyl, clinical features after their use are indistinguishable. In a series of eleven intoxications involving acrylfentanyl, patients were reported to have decreased consciousness, respiratory depression, and miosis with five patients requiring ICU admission (Helander et al., 2017). In addition, fentanyl analogs such as 4-fluorobutyrfentanyl, acetylfentanyl, furanylfentanyl, and ocfentanyl have been ruled as causes in numerous reported deaths (Rojkiewicz et al., 2016, Yonemitsu et al., 2016, Takase et al., 2016, Guerrieri et al., 2017, Mohr et al., 2017, Coopman et al., 2016). Uncommon adverse effects after usage of fentanyl analogs have been reported in the literature. Cole et al describe the case of an 18 year old boy who developed hypoxic respiratory failure and diffuse alveolar hemorrhage after insufflating what he thought was acetylfentanyl, but after analysis, was found to be butyrfentanyl (Cole et al., 2015).

6.1.3 Novel synthetic opioids

While novel synthetic opioids are structurally unrelated to morphine, they share analgesic and CNS depressant properties similar to it, including respiratory depression (Coopman et al., 2016, Papsun et al., 2016, Domanski et al., 2017). They are also associated with unwanted effects such as nasal burn or nasal drip

after insufflation, or a bitter taste after oral ingestion. Other common adverse symptoms include dizziness, nausea, vomiting, anxiety, sweating, and disorientation (Siddiqi et al., 2014). Three Swedish men, all with a history of recreational MT-45 use, developed folliculitis and dermatitis with hair loss, dry eyes, and elevated liver enzymes (Helander et al., 2017). Two of the patients had leukonychia striata (Mees' lines), typically found in thallium poisoning. The authors note that these patients did not present with signs and symptoms related to thallium toxicity, but do not offer a mechanistic explanation for the nail findings. While most symptoms gradually disappeared in this cohort, two developed severe bilateral cataracts requiring surgery. It is unclear if this constellation of findings was related solely to MT-45 or another contaminant. MT-45 may also be associated with delayed bilateral hearing loss, as reported in the case of three patients (Helander et al., 2014). Deaths have been reported in the literature with varying post-mortem serum and urine concentrations but again, with little consistency in patient case data, such data is not amenable to extrapolation into clinical care of the novel synthetic opioid-poisoned patient (Elliott et al., 2016, Papsun et al., 2016, Dziadosz et al., 2017, McIntyre et al., 2017).

6.2 Treatment

Initial care of the opioid intoxicated patient should focus on protecting the airway and maintaining breathing and circulation as in any emergency situation. Concurrently, preparations need to be made to administer naloxone as soon as possible. Naloxone, a competitive μ -opioid receptor antagonist, reverses central

and peripheral opioid effects rapidly. Naloxone can be administered via any route: intravenous, intramuscular, intranasal, subcutaneous, endotracheal, inhalational and sublingual (Kim and Nelson, 2015). Due to extensive first-pass metabolism leading to low oral bioavailability, parenteral routes have often been the routes of choice with an onset of action of 30 seconds for intravenous to 5 minutes for subcutaneous routes. Ease of administration and a lower risk of needle stick injury by administering personnel have led to the intranasal route gaining favor in the layperson and prehospital setting. In addition to the route of administration, naloxone effectiveness and duration of action depends on the type and dose of the opioid involved, and typically does not remain effective past 90 minutes (Kim and Nelson, 2015). Recommended starting doses to reverse opioid-induced respiratory depression range from 0.04-2 mg depending on the reference consulted. Very low doses below 0.1 mg are thought to reverse life-threatening respiratory depression without precipitating acute opioid withdrawal, which although not usually life threatening in an adult, is an extremely uncomfortable process. However, these recommendations do not take into account inadvertent fentanyl overdoses, which may require far more than the usual naloxone dose to reverse the effects.

Recent literature has advised that for heroin-induced respiratory depression, patients do not necessarily need to be transported to the ED and can be safely discharged home after a one-hour observation period (Willman et al., 2017). Although this treatment plan may be adequate for heroin, we do not recommend it for synthetic opioids. Fentanyl, fentanyl analogs and novel

synthetic opioids require larger and sometimes repeated doses of naloxone to effectively reverse respiratory depression. Due to recrudescence of symptoms when naloxone wears off, a longer observation period may also be required. In interviews with 64 illicit opioid users who had witnessed or experienced an opioid overdose in the previous 6 months in Massachusetts, 75% witnessed the administration of naloxone, gave naloxone to someone, or received naloxone themselves. Of these, 83% reported needing 2 or more naloxone doses before a response was seen (2 mg IN per dose). During the study time period, fentanyl was the primary illicit opioid in the state (Somerville et al., 2017). During the 2006 fentanyl outbreak, naloxone was given in 26/55 (47.3%) of ED visits in one study cohort. Doses ranged from 0.4-12 mg, with 6 cases requiring naloxone doses of at least 6 mg to reverse respiratory depression (Schumann et al., 2008). A 0.4 mg dose was only effective in 15% of cases requiring naloxone. In a series of 18 patients exposed to counterfeit acetaminophen/hydrocodone pills which actually contained fentanyl, 17 required naloxone, ranging from 0.4-8 mg IV boluses. Four of these cases required naloxone infusions lasting 26.3-39.7 hours. One of these patients required repeat naloxone bolus and infusion 8 hours after the initial naloxone infusion was stopped (Sutter et al., 2017). Fentanyl analogs such as acrylfentanyl, 4F-iBF, and acetylfentanyl have also required additional naloxone boluses or continuous infusion (Helander et al., 2017a, Rogers et al., 2016). Carfentanil toxicity due to illicit drug use has been reported in the lay press, causing deaths in Ohio, Maryland, Pennsylvania, and other states since 2016 (Gussow, 2016). Information in the medical literature is sparse, and the only

human toxicity report is in a veterinarian accidentally splashed in the eyes and mouth with carfentanil. In the prehospital setting, he received 100 mg naltrexone parenterally (packaged with the veterinarian carfentanil kit) and was observed in the hospital for 24 hours without complications (George et al., 2010). Anecdotally, carfentanil is requiring many doses of naloxone to reverse the opioid effects, up to 18 mg in one report (Gussow, 2016). Due to its extremely high potency and lack of human pharmacokinetic and clinical overdose knowledge, we recommend that all carfentanil cases be monitored for 24 hours in the hospital setting until more clinical cases are reported.

Other novel synthetic opioids such as U-47700 and MT-45 have responded well to traditional doses of naloxone. In 5 confirmed U-47700 cases, 2 did not require any naloxone (Domanski et al., 2017), 1 improved with 0.4 mg IV naloxone (Armenian et al., 2017), 1 improved with 2 mg IV naloxone (Schneir et al., 2017), and only one required two 2 mg doses of naloxone for a response (Jones et al., 2017). In a case series of 9 MT-45 cases, 7 were given naloxone in doses ranging from 0.1-2.0 mg IV. Three of those cases needed additional doses, but none of the total doses exceeded 2 mg (Helander et al., 2014).

The high prevalence of opioid abuse in the US, combined with the threat of synthetic opioids, makes it so that layperson and first responder naloxone access is imperative (Doyon et al., 2014). With the FDA's assistance, naloxone is now available over the counter, that is, without a provider's prescription, in 40 states (Gupta et al., 2016). The FDA recently approved a 2 mg injectable naloxone preparation, because of the concern that the previously available 0.4

mg autoinjector is not sufficient to reverse synthetic opioid toxicity (FDA, 2016). In addition to availability, the rising price of naloxone is an inhibitor to its use and distribution (Gupta et al., 2016).

7. Conclusion

As the opioid crisis worsens globally, emergence of fentanyl, fentanyl analogs and novel synthetic opioids are posing a serious threat to the population at large. The rapid emergence of new compounds, primarily from Chinese suppliers, makes analytical detection difficult and newer techniques such as LC-HRMS invaluable in identifying novel opioids. As specific compounds are made illegal (Schedule I in US), new analogs and novel synthetic opioids are emerging onto drug markets at a faster pace. More potent than morphine and heroin, fentanyls cause profound respiratory and CNS depression which may cause death in the unsuspecting user. Many of the synthetic opioids mentioned in this review require larger doses of naloxone to reverse than heroin. In the case of a suspected synthetic opioid intoxication, we advise clinicians to use repeated and increasing doses of naloxone to elicit a response.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Synthetic Opioid	DEA (US)	Date (DEA)	UN
alpha-methylfentanyl	Schedule I	9/22/1981	Schedule I
sufentanil	Schedule II	5/25/1984	Schedule I
3-methylfentanyl	Schedule I	9/22/1986	Schedule I
alfentanil	Schedule II	1/23/1987	Schedule I
3-methylthiofentanyl	Schedule I	5/29/1987	Schedule I
acetyl-alpha-methylfentanyl	Schedule I	5/29/1987	Schedule I
alpha-methylthiofentanyl	Schedule I	5/29/1987	Schedule I

Table 1. DEA and UN scheduling of synthetic opioids

Synthetic Opioid	DEA (US)	Date (DEA)	UN
beta-hydroxyfentanyl	Schedule I	5/29/1987	Schedule I
para-fluorofentanyl	Schedule I	5/29/1987	Schedule I
thiofentanyl	Schedule I	5/29/1987	Schedule I
beta-hydroxy-3-methylfentanyl	Schedule I	1/8/1988	Schedule I
carfentanil	Schedule II	10/28/1988	NS
remifentanil	Schedule II	11/5/1996	Schedule I
acetyl fentanyl	Schedule I	7/17/2015	Schedule I
beta-hydroxythiofentanyl	Schedule I	5/12/2016	NS
butyryl fentanyl	Schedule I	5/12/2016	NS
AH-7921	Schedule I	5/15/2016	Schedule I
thiafentanil	Schedule II	8/26/2016	NS
U-47700	Schedule I	11/14/2016	NS
furanyl fentanyl	Schedule I	11/29/2016	NS
4-fluoroisobutyryl fentanyl	Schedule I	5/3/2017	NS
MT-45	NS		Schedule I

NS- not scheduled

Appendix 1. Search strategy details.

Date Searched	Database searched	Search terms	Number of results
4/28/17	PubMed	("fentanyl analog" OR "fentanyl analogues" OR "fentanyl analogs" OR "fentanyl analogue" OR "fentanyl- contaminated" OR "fentanyl laced" OR "fentanyl derivative" OR "fentanyl-derived" OR "fentanyl derivatives" OR "acetyl fentanyl" OR acetylfentanyl OR furanylfentanyl OR "furanyl fentanyl" OR butyrfentanyl OR butyryl fentanyl OR butyrylfentanyl OR fluorobutyrfentanyl OR 4-fluorobutyrfentanyl	404

		<p>OR para- fluorobutyrfentanyl OR B-OH-thiofentanyl OR fluorobutyrylfentanyl OR butyrfentanyl OR beta-hydroxy-fentanyl OR beta-hydroxy- fentanyls OR methylfentanyl OR 3- methylfentanyl OR fluorofentanyl OR p- fluorofentanyl OR methoxybutyrfentanyl OR 4- methoxybutyrfentanyl OR acrylfentanyl OR U-47700[tij] OR U- 50488[tij] OR AH- 7921[tij] OR MT-45[tij] OR W18[tij] OR W- 18[tij] OR 4- chloroisobutyrfentanyl OR 4Cl-iBF OR 4-</p>	
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		<p>fluoroisobutyrfentanyl OR 4F-iBF OR tetrahydrofuranfentanyl I OR THF-F OR cyclopentylfentanyl OR “China white” OR “synthetic heroin” OR (fentanyl[ti] AND (designer[ti] OR non- pharmaceutical[tiab] OR analog[ti] OR analogs[ti] OR analogue[ti] OR analogues[ti] OR illicit[tiab] OR overdose)) OR (carfentanil AND (abuse OR overdose OR misuse OR overuse OR mortality OR death OR deaths) NOT (pet OR positron)) AND</p>	
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		English[lang]	
5/3/17	Google	carfentanil AND "report" site:.gov	20
5/3/17	Google	(U-47700 OR U-50488 OR AH-7921 OR MT- 45 OR W18 OR "synthetic opioid" OR "synthetic opioids") AND "report" site:.gov	20
5/3/17	Google News	fentanyl OR U-47700 OR U-50488 OR AH- 7921 OR MT-45 OR W18 OR 4- chloroisobutyrfentanyl OR 4Cl-iBF OR 4- fluoroisobutyrfentanyl OR 4F-iBF OR tetrahydrofuranfentany l OR THF-F OR cyclopentylfentanyl OR carfentanil OR "synthetic opioid" OR "synthetic opioids"	50
5/26/17	Google	"pill die mold" OR "pill die molds" OR "pill die	60

		<p>mold Watson 853” OR “pill die mold Norco” OR “pill die mold R039” OR “pill die mold Xanax” OR “pill die mold M30” OR “pill die mold A215” OR “pill die mold oxycodone” OR “pill die mold G74” OR “pill die mold oxymorphone” OR “pill die mold V3601” OR “pill die mold Watson 853” OR “pill die mold hydrocodone” OR “pill die mold M523” OR “pill die mold oxycodone” OR “pill press” OR “pill presses” OR “pill press Watson 853” OR “pill press Norco” OR “pill</p>	
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		<p>press R039" OR "pill press Xanax" OR "pill press M30" OR "pill press A215" OR "pill press oxycodone" OR "pill press G74" OR "pill press oxymorphone" OR "pill press V3601" OR "pill press Watson 853" OR "pill press hydrocodone" OR "pill press M523" OR "pill press oxycodone"</p>	
5/26/17	Google	<p>"Research chemicals USA" OR "research chemical" OR "research chemical buy" OR "fentanyl buy" OR "research chemical opioid" OR "research chemical opioid buy" OR "carfentanil buy" OR "U-47700 buy" OR</p>	50

		"MT-45 buy" OR "fentanyl analog buy"	
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