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“Gray Death”—The Trojan Horse of the Opioid Epidemic: Historical, Clinical, and Safety Evidence for the Clinical Nurse Specialist

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Article Content

In 2017, a new opioid configuration emerged in the United States called "gray death." This illicit opioid has an appearance similar to dry concrete mix or a rock. Indiana, Ohio, Georgia, and Alabama have reported deaths with the use ultradangerous combinations of fentanyl, carfentanil, and U-47700, and reports are multiplying across the United States.¹ This article explores the current outbreak of fentanyl-related overdoses in the United States and the

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world. The most current safety recommendations (known at this time) for clinicians providing care for persons abusing fentanyl and fentanyl-related compounds such as “gray death” will be provided.

THE ALLURE OF FENTANYL

During the past 40 years, the United States has experienced 3 fentanyl epidemics. During the 1970s, fentanyl and fentanyl-related compounds from China were responsible for hundreds of deaths in the United States. This first epidemic resulted in the implementation of the Controlled Substances Analog Enforcement Act of 1986. From 2005 to 2007, nearly 1000 persons died during a second epidemic of illicit fentanyl brought into the United States from illegal laboratories in Mexico. The current fentanyl outbreak began in 2013. Carfentanil has also arrived during this third wave and is responsible for nearly 400 overdose cases in 2016, with 84% of these cases occurring in the state of Ohio.²

Introduced 50 years ago, fentanyl has become the most used opioid for intraoperative anesthesia in North and South America, Europe, the Middle East, and in developed Africa and Asia. In the 1990s, use of fentanyl was expanded beyond surgery for the management of cancer pain and treatment of chronic pain. Intravenous fentanyl facilitates rapid anesthesia induction, results in less hemodynamic instability, has minimal cardiovascular adverse effects, and does not increase plasma histamines such as morphine and meperidine. Metabolized via the human cytochrome P450 (CYP3A4) isoenzyme system, onset of action and peak plasma concentrations are a function of the dosage used and method of delivery.³ In addition, fentanyl and fentanyl-related analogs have high lipid solubility. As a result, fentanyl drug can be delivered in a variety of slow release pathways such as the skin, mucous membranes, or the mouth and only small amounts of drug are needed because access to the brain is so immediate.¹

WORLDWIDE FENTANYL EXPERIENCE

The United States is not alone in this opioid crisis. Since 2011, Germany, Finland, and the United Kingdom have also experienced outbreaks of fentanyl-related deaths. Diversion from regulated supply chains and illicit production in response to heroin shortages in Bulgaria and Slovakia have fueled the European crisis. Diversion includes inappropriate or overprescribing of opioids, pharmacy theft, sale of unused fentanyl patches, as well as misuse and sale by healthcare providers. Dark sources of fentanyl are the discarded patches retrieved from hospital and nursing home waste containers. Drug is extracted from the patch and placed in liquid for injection or inhalation. The patch is also smoked on foil, placed directly on the skin, or cut into pieces to be sucked or swallowed.⁴

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...weaponized fentanyl than using a lethal chemical agent, because the Russian military used a combination of an aerosolized fentanyl or fentanyl derivatives with an inhalation anesthetic to incapacitate Chechen rebels, holding 800 hostages at a Moscow theater in October 2002. To save hostages who were likely to be killed and incapacitate rebels, a "calmative" agent was used in the theater described as "not lethal." However, 127 of the 800 hostages died and more than 650 required hospital admission with what was diagnosed as "sleeping gas" poisoning. Treatment for opioid poisoning was delayed because components of the gas were unknown by the clinicians who tried a variety of antidotes base on the belief that a "nerve gas" was used before using naloxone.⁵

Illicit production of fentanyl is not confined to Mexico or China. Beginning in 1990, the first illicit fentanyl was produced in Kansas, which resulted in the seizure of 2 illicit laboratories. From 2000 to 2005, several illicit laboratories in the United States were also closed. Because fentanyl is more potent than heroin, demand is increasing and profit margins are expanding.⁶

Today, opioids have become the most common element in overdose deaths in the United States with 33 091 in 2015, with nearly 10 000 deaths of these deaths related to synthetic opioids (fentanyl and fentanyl-related products other than methadone). China and Mexico remain the primary sources for illicit fentanyl production and distribution in the United States. Vast and effective distribution is accomplished through sales through the World Wide Web, dark web, and mail and via the interstate highway system from Mexico and Canada.⁶

The effects of opioid trafficking on public health are dreadful. Overdose deaths are defined as deaths from unintentional or intentional overdose of a drug, receiving the wrong drug, or taking a drug in error. Natural and semisynthetic opioids include morphine, codeine, hydrocodone, and oxycodone. Synthetic opioids excluding methadone include fentanyl, fentanyl analogs, and tramadol.⁷

Data provided in Table 1 describe the age-adjusted rates of drug overdose deaths per 100 000 non-Hispanic black and white persons and Hispanic persons.⁷Table 2 data describe the shift in opioid type in overdose deaths from 2010 to 2015.⁷ In addition, for 2015, the percentage of drug overdose deaths involving heroin tripled compared with 2010. Although drug overdose death rates increased for all age groups, the greatest percentage increase was among adults aged 55 to 64 years. The highest rate for overdose deaths in 2015 was for adults aged 45 to 54 years (30 deaths per 100 000). The 4 states with the highest age-adjusted drug overdose rates were West Virginia, New Hampshire, Kentucky, and Ohio.⁷

Articles & Publications **CE Connection** Clinical Resources **Table 1** Age-Adjusted Rate of Drug Overdose Deaths per 100,000

Persons	1999	2015	Change per Year, %	Percent Increase, %
Non-Hispanic white persons	0.2	2.1	7	1240
Non-Hispanic black persons	7.5	12.2	2	163
Hispanic persons	5.4	7.7	2	143

Drug	2010, %	2015, %
Natural and semisynthetic opioids	29	24
Methodone	12	6
Heroin	8	25
Synthetic opioids other than methadone	8	18

Table 2 Changes in Drugs Used in Overdose Deaths 2010 and 2015

Data suggest that opioid fatalities have increased in great part from the *increasing availability of synthetic opioids and heroin*. Fentanyl (50 times as potent as heroin) and carfentanil (5000 times as potent as heroin) are increasingly laced into heroin, increasing the risk of overdose and death even when naloxone is available. Naloxone is often ineffective or short acting depending on the amount, route, and type of opioid used.⁸

CARFENTANIL-DEATH DISGUISED AS A FEW GRAINS OF POWDER

Carfentanil (formally known as Wildnil) is a synthetic fentanyl derivative related to fentanyl and sufentanil. Commercial production of Wildnil stopped in 2002 and available as a compound dosage for veterinary use. Carfentanil is used for chemical capture and rapid of large animals in zoos and wildlife areas for examination and treatment. One hundred times more potent than fentanyl and 10 000 times more potent than morphine, carfentanil is usually delivered via a dart intramuscularly. Personal protective gear is required when used to prevent accidental absorption through mucus membranes in the eyes, nose, mouth, or through broken skin, which can result in rapid onset opioid toxicity. Signs and symptoms include pinpoint pupils, respiratory depression, depressed mental state, lethargy, sedation, nausea, vomiting, apnea, and cardiac arrest. The lethal dose for humans is unknown. Limited case studies suggest a time line of minutes for intervention after face, eyes, or mouth exposure. Naltrexone hydrochloride is veterinary antidote for carfentanil exposure, which has an antagonistic potency twice that of naloxone.^{9,10}

The emergence of carfentanil in illicit drug production has significantly increased the number of overdoses and overdose-related deaths even among opioid tolerant users. Carfentanil is found in many forms including powder, blotter paper, tablets, patches, and spray and can resemble powdered cocaine or heroin. Routes of consumption include inhaled, injection, rectal, intranasal, transdermal, and transmucosal. Carfentanil and fentanyl analogs pose significant threats to safety for first responder medical and laboratory personnels.^{11,12} Other street names include *Aunt Hazel, Emma, Batman, China Cat, Dead on Arrival, Elephant, Foo Foo Stuff, Heaven Dust, Sack, Salt, Red Chicken, Reindeer Dust, Skag, Sweet Dreams, The Beast, The Witch, Tiger, White Lady, White Nurse, and Zero*. "Body stuffers" or persons who conceal these

U-47700

To provide an even more powerful illicit opioid combination, U-47700 has emerged mixed with heroin and fentanyl or fentanyl and carfentanil, creating "gray death."^{1,13} "Gray death" seems similar to concrete mixing powder and texture ranges from chunky rocklike material to fine powder and can be injected, eaten, or smoked. At this time, it is unknown how U-47700 interacts with fentanyl, carfentanil, or heroin in the body.¹³ Some of the pills taken from Prince's estate after the musician's overdose death last year contained U-47700.¹⁴

U-47700 is another synthetic opioid, with an abuse potential similar to heroin, prescription opioids, and other synthetic opioids. The drug comes in powder form and in counterfeit tablets that look like pharmaceutical opioids. The drug is sold as single agent and in combinations previously described. Because U-47700 is produced in illicit laboratories outside the United States, purity and dosage are often unknown, creating a "Russian Roulette" scenario for any user.¹⁵

U-47700 has been a legal alternative to fentanyl in China and a potent fentanyl derivative not unlike carfentanil.¹⁴ In 2016, the US Drug Enforcement Administration (DEA) placed U-47700 into Schedule I of the Controlled Substances Act, in response to reports regarding this lethal new street drug. The DEA action was based on reports of 46 deaths associated with use, 31 in New York and 10 in North Carolina. From October 2015 to September 2016, the DEA received 88 reports from forensic laboratories of U-47700 detection. This DEA action will last for 24 months and may be extended 12 months if further data is required to permanently schedule U-47700.¹⁵

RESPONDING TO OVERDOSE AND EXPOSURE

The cornerstone of care for overdose is the reversal agent naloxone (Narcan, Bristol-Myers Squibb, New York), 10 mg intravenous (IV) which can be repeated in 1 minute and then every 3 to 5 minutes until breathing without assistance for 15 minutes.^{9,11} Consider decontamination if patient presents within 1 hour of oral ingestion with gastric lavage, activated charcoal *but only with a protected airway*. Evidence supporting this intervention *is very weak* in light of the risks of aspiration and lack of efficacy. As a result, this intervention is *not* routinely recommended. Intravenous naloxone is the preferred route administration for adults and children. For adults without IV access, other routes include intramuscular (IM), subcutaneous (SQ), and intranasal. Off-label endotracheal installation is the least desirable route based on

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anecdotal evidence. Naloxone can also be given to adults via nebulizer (adults only) and introsseous (IO) when preferred access is not available. For pediatric treatment, IO administration is considered an off-label use. Although naloxone can be given IM, SQ, or endotracheal (also considered off-label use), onset of action will be delayed compared with IV administration. Supportive therapies include intravenous fluids and vasopressors if response to fluids is poor, benzodiazepines for seizures, and surgery if necessary for body packers with acute poisoning, gastrointestinal obstruction, or perforation.¹²

Respiration should be continuously monitored particularly because naloxone effects range from 20 to 60 minutes and multiple doses are often needed for synthetic opioid combinations. Consider chest radiography for patients with pulmonary signs and symptoms to rule out noncardiogenic pulmonary edema that can occur with abuse of synthetic opioid combinations. Hospital admission should be considered with pediatric ingestion, use of long-acting opioids, and continued respiratory depression with treatment. Body packers should be admitted to the intensive care unit.¹²

Some drug combinations, particularly laced with carfentanil, can be absorbed through the skin or inhaled accidentally during emergency care. Onset of signs and symptoms usually occur within minutes of exposure and include respiratory depression or arrest, drowsiness, disorientation, sedation, pinpoint pupils, and clammy skin. *Do not use hand sanitizers* for skin contact that contain alcohol (a skin penetrant), which may increase the absorption of fentanyl through the skin. Wash hands with copious amounts of soap and cool water. Do not disturb any substance that may be drug unless the proper protective equipment is used and naloxone is readily available. Never eat, drink, or smoke in the presence of possible drugs.⁶

With regard to use of gloves, while the permeation rate of fentanyl through nitrile is unknown, the National Institute for Occupational Safety and Health (NIOSH) recommends wearing nitrile gloves (minimum thickness of 5 mil), doubled and powder free, when handling fentanyl-related compounds because nitrile demonstrates low permeability to other hazardous drug compounds. Powdered gloves should be avoided because the powder may absorb narcotic particulates and increase dermal contact and dermal absorption during removal. Gloves should be changed every 30 to 60 minutes of use. If necessary, outer gloves can be removed and inner gloves can be used to label evidence if needed. Hands must be washed immediately with soap and cool water. Black gloves may be used to better visualize any powder residue and use of 2 colors for double gloving can help the clinician better visualize any holes or tears for further protection.¹⁶

MOVING FORWARD

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Opioid addiction or opioid use disorder is a chronic relapsing illness requiring sustained treatment, often for years to achieve and sustain recovery. Limited access to addiction specialists and programs, limited access to social support and social stigma are significant barriers to recovery. Pharmacological resources for this battle are slim; methadone, buprenorphine, and extended release naltrexone. New medications on the horizon include agents to support compliance with therapy and reduce risks for diversion and agents to modulate reward circuits, withdrawal pathways, and craving.⁷

Collaboration between the National Institutes of Health and private partners currently focus on 3 specific areas: development of improved overdose-reversal agents and preventative interventions to decrease mortality, saving lives for treatment and recovery from opioid addiction with new pharmacological and technological treatments, and the development of safe, effective, and nonaddictive interventions to manage chronic pain.⁷

Initial work has begun. In 2015, the Food and Drug Administration approved an easy-to-use intranasal naloxone that provides blood levels of naloxone comparable with parenteral administration. This new treatment option was developed through partnership of the National Institute on Drug Abuse and industry. In collaboration with private partners, work is in progress to develop more powerful, longer-acting opioid antagonists. Vaccines for prescription opioids, heroin, and fentanyl are also on the horizon, designed to induce antibody production to prevent opioids entering the brain. Monoclonal antibodies may help prevent overdoses and relapses. Finally, development of new options to manage chronic pain without opioids have promise and include cannabinoids, tetrahydrocannabinol, dopamine D3 antagonists, tumor necrosis factor inhibitors, brain stimulation technologies, and gene therapies.⁷

DOSING GUIDELINES FOR OPIOID PRESCRIBING

The "perfect storm" leading to the present opioid crisis began in the 1980s and through the 1990s. The "mantra" during these years was that pain was being poorly treated. The result was endless education regarding treatments for pain, adoption of pain as a vital sign, and ultimately linking patient satisfaction surveys to physician and nursing performance score cards and, in some cases, reimbursement. However, the reality was that the perfect storm lacked concrete evidence to support treatment of long-term pain for diagnoses outside cancer and palliative care. Prescribers were caught in the storm of improving patient satisfaction rather than screening for addiction and calculating the risk-benefits of opioid therapy.¹⁷ Finally, a lifeboat has appeared for clinicians trying to treat pain.

The Centers for Disease Control and Prevention (CDC) 2016 recommendations for opioid

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prescribing may be the most important documents for primary care clinicians for prescribing opioids for chronic pain outside cancer and palliative care.^{17,18} Recommendations include to consider prescribing opioids only if benefit outweighs risk, use the lowest effective dose, combine therapy with nonpharmacological treatments and nonopioid drug therapy when possible, and avoid prescribing with benzodiazepines whenever possible and consider prescribing naloxone where there is risk of overdose.¹⁸

THE FUTURE

Widespread adoption of the 2016 CDC guidelines could help begin to bring to an end to the current epidemic of opioid overprescribing. Additional strategies should include correcting the gaps in insurance coverage for the treatment of chronic pain and addiction and reimbursement for nonpharmacological interventions. Essential to move forward is support for medication-assisted therapies for opioid addiction such as methadone and buprenorphine. Rather than assuming that this drug therapy is trading 1 addiction for another, consider that these medications allow patient to live and manage their disease not unlike a person with diabetes who takes insulin. Finally, education and training for clinicians in schools and in practice should be considered as the requirement to prescribe opioids.¹⁷

Finally, prescribers and patients need to acknowledge the elephant in the room. Only time will reveal how much constant and misleading pharmaceutical advertising has contributed to the current crisis. Pharmaceutical advertising and education in the in the 1980s and 1990s minimized the risk for misuse and addiction and helped create a culture of compulsory generous opioid prescribing.¹⁹ Clinicians who voiced fears of addiction and misuse or prescribed modest doses were perceived as practicing in an outdated, narrow-minded, nonevidence-based way. Looking back now, one can see how this marketing disguised as evidence led clinicians and patients to where we are standing now.

The 2016 CDC guidelines provide a beginning for the way out of this current crisis. For the future, qualitative research is needed to understand motivations for opioid use and forces for relapse.^{4,20} Finally, perhaps clinicians and patients should rethink their perceptions regarding pain. Compassion does not mean the elimination of all pain and the reduction of suffering is much more complex than just prescribing opioids.²⁰

For additional safety information, check out the following resources available on the World Wide Web.¹¹

CDC Health Advisory (#CDCHAN-00384): <http://emergency.cdc.gov/han/han00384.asp>

CDC Health Update (#CDCHAN-00395): <http://emergency.cdc.gov/han/han00395.asp>

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DEA fentanyl warning video:https://www.dea.gov/video_clips/Fentanyl%20Roll%20Call%20Video.mp4

References

1. Mammoser G. 'Grey death' is the latest dangerous street drug. Healthline Web site. <http://www.healthline.com/health-news/gray-death-latest-dangerous-street-drug>. Accessed July 17, 2017. [Context Link]
2. Casale JF, Mallette JR, Guest EM. Analysis of illicit carfentanil: emergence of the death dragon. *Forensic Chem.* 2017;2017:74-80. [Context Link]
3. Stanley TH. The fentanyl story. *J Pain.* 2014;15(12):1215-1226. [Context Link]
4. Mounteney J, Giraudon I, Denissov G, Griffiths P. Fentanyls: are we missing the signs? Highly potent and on the rise in Europe. *Int J Drug Policy.* 2015;26(7):626-631. [Context Link]
5. Wax PM, Becker CE, Curry SC. Unexpected "gas" casualties in Moscow: a medical toxicology perspective. *Ann Emerg Med.* 2003;41(5):700-705. [Context Link]
6. US Department of Justice, Drug Enforcement Administration. *Fentanyl: A Briefing Guide for First Responders*. Drug Enforcement Administration Web site. https://www.dea.gov/druginfo/Fentanyl_BriefingGuideforFirstResponders_June2017.p. Accessed July 18, 2017. [Context Link]
7. Hedegaard H, Warner M, Minino M. Drug overdose deaths in the United States, 1999-2015. *NCHS Data Brief, no. 273*. National Center for Health Statistics: Hyattsville, MD; 2017. [Context Link]
8. Volkow ND, Collins FS. The role of science addressing the opioid crisis. *N Engl J Med.* 2017;377:391-394. Available at <http://www.nejm.org/doi/full/10.1056/NEJMs1706626#t=article>. Accessed July 6, 2017. [Context Link]
9. Lust L, Barthold C, Malesker M, Wichman T. Human health hazards of veterinary medications: information for emergency departments. *J Emerg Med.* 2011;40(2):198-207. [Context Link]
10. George AV, Lu JJ, Pisano MV, et al. Carfentanil—an ultra potent opioid. *Am J Emerg Med.* 2010;28(4):530-532. [Context Link]
11. United States Department of Justice, Drug Enforcement Administration. *Carfentanil: a Dangerous New Factor in the Opioid Crisis*. Drug Enforcement Administration Web site. https://www.dea.gov/divisions/hq/2016/hq092216_attach.pdf. Accessed September 1, 2017. [Context Link]

12. Lexicomp Online, Opioids (Lexi-Comp), Lexi-Comp Online, Hudson, Ohio, Wolters Kluwer Clinical Drug Information, Inc. : 2016. <http://www.wolterskluwer.com/lexicomp-online/>. Accessed July 15, 2017. [Context Link]

13. Murphy M. Emerging trend bulletin: potent new opioid/opiate compound known as "Grey Death". *Gulf Coast HIDTA investigative Support Network* Massachusetts Technical Assistance Partnership for Prevention Web site. <http://masstapp.edc.org/sites/masstapp.edc.org/files/Grey-Death-GCHIDTA-0517.pdf>. Accessed July 17, 2017. [Context Link]

14. Watt L. China bans more synthetic opioids blamed for US drug deaths. *The Seattle Times* Web site. <http://www.seattletimes.com/nation-world/china-bans-more-deadly-synthetic-opioid>. Accessed July 20, 2017. [Context Link]

15. Drug Enforcement Administration.. *DEA schedules deadly synthetic drug U-47700*. Drug Enforcement Administration. Web site. <https://www.dea.gov/divisions/hq/2016/hq111016.shtml>. Accessed July 20, 2017. [Context Link]

16. National Institute for Occupational Safety and Health. Fentanyl: preventing occupational exposure to emergency responders. Centers for Disease Control and Prevention Web site. <https://www.cdc.gov/niosh/topics/fentanyl/risk.html>. Accessed July 19, 2017. [Context Link]

17. Olsen Y. The CDC guideline on opioid prescribing: rising to the challenge. *JAMA*. 2016;315(15):1577-1579. [Context Link]

18. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016. *MMWR Recomm Rep*. 2016;65(1):1-49. [Context Link]

19. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559-574. [Context Link]

20. Lee T. Zero pain is not the goal. *JAMA*. 2016;315(15):1575-1577. [Context Link]

