Chair Bass, Vice-Chair Demings, Ranking Member Ratcliffe and other distinguished members of the House Subcommittee on Crime, Terrorism and Homeland Security, thank you very much for the opportunity to testify before you today. It is indeed an honor to be here. My name is Dan Ciccarone. I am professor of family and community medicine at the University of California, San Francisco. I have been a clinician for over 30 years and an academic researcher in the area of substance use with a focus on the medical and public health consequences of heroin use for the past 20 years. I have been asked to speak on my perspective on the class scheduling of fentanyl analogues and how these regulations might work counter to the goals of public health.

My research and that of my team is multidisciplinary and multi-level. We use the tools of epidemiology, anthropology, statistics, economics, clinical and basic sciences. I am appreciative of my funder, which is the National Institutes of Health, National Institute on Drug Abuse, as well as my team, which includes Dr. Jay Unick, University of Maryland, Dr. Sarah G. Mars, UCSF, Dr. Dan Rosenblum, Dalhousie University, and Dr. Georgiy Bobashev from RTI, North Carolina.

I know the current overdose epidemic first hand. I have witnessed it at the ground level in my street-based ethnographic research. My team and I have published extensively on the opioid overdose crisis. In this testimony I will discuss the public health dimensions of the triple wave opioid overdose crisis, give a primer on the fentanyl class of opioids, and present the challenges of drug supply control esp. as they relate to fentanyl, as well as the opportunities presented by drug policy reform and demand reduction.

Overdose deaths due to illicit fentanyl represent a historic crisis; one full of challenges. But, this era is also one of historic opportunity: to rebalance our drug policies more in favor of demand reduction, including treatment, and away from failed prohibitionist policies; and to reorient to a healthier society resilient to problematic drug use.
**A Drug Crisis of Historic Proportions**

For the first time in 100 years, life expectancy at birth has gone down in the US three years in a row from 2014 to 2017. In 1919, mortality rates shot up because of the ravages of WW1 and the great influenza pandemic. And because these events disproportionately affected young people, correspondingly life expectancy went down. While we don’t have a war of similar scale or infectious epidemic affecting young people today we do have another scourge: drug poisoning which is disproportionately affecting young people and driving down life expectancy. According to the latest formal data from the US Centers for Disease Control and Prevention (CDC), deaths due to drug poisoning exceeded 70,000 in 2017; with a 9.6% increase in drug mortality rate from 2016. Since the beginning of the opioid epidemic 700,000 Americans have died from drug poisoning. Annual deaths due to drug overdoses now exceed deaths due to car accidents, gun violence, and even HIV at the height of the 1990’s HIV epidemic.

**The triple wave epidemic**

The triple wave epidemic of overdose deaths stems from three classes of opioids: prescription opioid pills ("semi-synthetic opioids" in Figure 1), heroin and synthetic opioids other than methadone. Figure 1 shows three waves of opioid mortality, each wave cresting on top of the one that preceded it.

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before it. In the first wave, overdoses related to opioid pills, started rising in the year 2000 and have steadily grown through 2016. The second wave saw overdose deaths due to heroin, which started increasing clearly in 2007, surpassing the number of deaths due to opioid pills in 2015. The third wave of mortality has arisen from fentanyl, fentanyl analogues and other illicit synthetic opioids in the drug supply, climbing slowly at first, but dramatically after 2013. Data from 2017 show synthetic opioid deaths continuing to rise, reaching a peak of over 28,000, while opioid pill and heroin overdose deaths leveled off, albeit at very high levels of approximately 15,000 deaths in each category.\footnote{Hedegaard H, Miniño AM, and Warner M, Drug overdose deaths in the United States, 1999-2017, in NCHS Data Brief no 329. Hyattsville, MD: National Center for Health Statistics. 2018.}

It is important to note that the latest provisional data from the US Centers from Disease Control and Prevention (CDC) shows the third wave – deaths due to fentanyls – continuing to rise with 32,299 deaths attributed to synthetic opioids in the 12-months period through June of 2019; an 8.3% increase from the 12-month period prior to June 2018.\footnote{https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed 1.22.20}

Understanding fentanyls

Opioids are put into three classes based on their relationship to opium: Natural, semi-synthetic and synthetic. Natural opioids are derived from opium, a gum extract of the poppy ovary; examples include morphine and codeine. Semisynthetics are derived from opium derivatives e.g. morphine or thebaine; examples include well known pharmaceutical opioids e.g. hydromorphone or oxycodone. Synthetics have no relationship to opium-based products and are produced in pharmaceutical facilities. Examples include fentanyl and methadone. Another way to classify opioids is by their mechanism of action at the mu-receptor of the nervous system: agonist, partial agonist and antagonist. Many pain medications as well as most opioids with abuse potential are full mu agonists. By triggering the mu-receptor they induce pain relief as well as euphoria. Partial agonists are just that, weaker stimulators of the mu-receptor. A good example of a partial agonist is the medication buprenorphine which is considered an excellent choice in treating opioid use disorder aka opioid addiction. Antagonists are essentially blockers of the mu-receptor and thus trigger no effect, except perhaps dislocating an agonist from mu binding and reversing its effect; the overdose reversal agent naloxone is a good example.

Fentanyl and its chemical cousins, the fentanyl analogues, are synthetic opioids. Mother chemical fentanyl is a powerful agonist with potency by volume 100 times that of morphine, 40 times that of heroin.\footnote{Ciccarone D. Fentanyl in the US heroin supply: A rapidly changing risk environment. Int J Drug Policy. 2017 08; 46:107-111. PMID: 28735776. PMCID: PMC5742018} As a licit medication fentanyl is successfully used in surgery, obstetrics and end-of life care; it has both short-acting and long acting forms which when applied correctly are tremendously useful. The street fentanyl that is causing the overdose crisis is illicitly manufactured product. According to the US Drug Enforcement Administration (DEA), illicit fentanyl is mostly coming from China.\footnote{US Drug Enforcement and Administration (2016). 2016 National Drug Threat Assessment Summary. Washington, DC: Domestic Strategic Intelligence Unit, Special Strategic Intelligence Section.} There is Estonian and Russian production, but those products do not come to the US. There have been waves of fentanyls into the US for three decades, the last one in 2006 in the Chicago region; however the recent wave, beginning in 2014 is the longest lasting.
Most of the illicit fentanyls are agonists and thus have abuse potential. It is important to note, however, that researchers have identified fentanyl analogues which are partial agonists and antagonists. In addition, importantly, one cannot predict which fentanyl analogue is going to be an agonist or an antagonist based on chemical structure alone.

My team and I have the privilege of doing some of our research in street-based settings talking to folks who use drugs and observing heroin, fentanyl and other drug use. This research helps gain a deep cultural understanding of drug use along with gaining the perspective of those most affected by the vicissitudes in supply and the structural risks that are imposed on them. From a public health perspective we are interested in understanding both imposed risk as well as behavioral risk taking. These understandings better inform interventions to reduce the negative health outcomes. We have written extensively on fentanyl supply, risk and perception. Among our findings: Fentanyls are a supply side phenomenon that was not driven by demand from heroin users; most street-based fentanyls are not sold as is, they are sold as fentanyl-adulterated or -substituted heroin (FASH); fentanyl adulteration is occurring unbeknownst to users and low-level dealers; FASH is the norm in the areas of the country with the highest overdose rates i.e. Midwest and New England regions; the fentanyl component of FASH is unpredictable and under constant change; as fentanyl supply changes, overdose risk changes. It is important to note that the cryptic nature of FASH and the resultant vicissitudes in heroin and fentanyl potency are likely driving overdose (more so than sheer potency alone). In addition, it appears likely that fentanyls appear to be here to stay; for a deadly chemical to stay around for 5 years says something about its durable supply.

PARADOXES OF PROHIBITION

The failure of drug prohibition

Drug policy is roughly divided into two poles: demand reduction and supply reduction. I have just stated that FASH is a supply side imposition into the US drug market. Since it is supply-sided then why not simply “turn off the tap? It’s not that I don’t believe in drug supply as problematic – I do and have written a number of papers on supply and the downstream problems it creates – it’s just that the reverse, i.e. attempting to decrease the problem by curtailing supply doesn’t work as

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well as we want it to and in fact having an excessive supply focus can have paradoxical results.

Supply control, including prohibition of drugs, and with the corollary penalization of drug use, has been the leading force in US drug policy for over a hundred years. The founding father of these prohibitionist efforts, beginning in the 1920s, was Henry Anslinger. President Richard Nixon famously coined the term “war on drugs” to highlight his efforts to curb the drug problem in the early 1970s. There is an extensive critical literature on the societal outcomes of this so-called war on drugs. I want to focus on one paper that is highly relevant to today’s discussion.

The journal *Science*, published by the American Association for the Advancement of Science (AAAS), is the most highly respected publication reporting on advances in scientific understandings in the world. Hawre Jalal and colleagues, reported in the September 21, 2018 issue of *Science* the results of their analysis of 38 years (1978 – 2016) of drug mortality data.\(^{17}\) They found an exponential growth in overdose deaths over this time period (Figure 2). This exponential increase in drug overdose deaths was not defined by any specific class of drugs. Each era has its

\[ y = 10^{0.038 + 0.032 \times (x - 1978)} \]

\[ R^2 = 0.99 \]

Figure 2. Mortality rates from unintentional drug overdoses. (A and B) Mortality rates for (A) individual drugs and (B) all drugs. Detailed data for individual drugs are only available from 1999 to 2016, although additional data for all drugs are available since 1979 (this area is grayed out). The exponential equation and fit are shown for all drugs. (Synth Opioids OTM: synthetic opioids other than methadone. This category includes fentanyl and its analogs.) From Jalal H, Buchanich J, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016, Science 21 Sep 2018:Vol. 361, Issue 6408, eaau1184. DOI: 10.1126/science.aau1184. Reprinted with permission from AAAS.

problematic drug defined by supply or by cultural desire, but the underlying driver of problematic drug use leading to death is independent of the type of drug and getting worse over time. Deaths due to opioids, including fentanyl, is only the latest manifestation of this multi-decade phenomenon. There is no doubt however that the triple wave has made the situation much worse.

The reasons for this ‘worse case’ public health scenario involves two failures: firstly, that of drug prohibition to curb the problem and secondly, the failure to address the underlying, root, causes of problematic drug use.

There is a metaphor we use in drug policy when discussing the paradoxical effects of many supply interventions: that of the ‘balloon’, i.e. attempts to restrict supply are like squeezing a balloon and, as we all know, that leads to the balloon popping out in an unexpected place. There are historical examples of supply control events with paradoxical effects. I’ll give just one example from my own research. In the 1990s and 2000s, the US led or supported intense efforts to reduce cocaine production in Colombia and export to the US. These efforts included crop spraying and supply route interdiction as well as arrest, extradition and supported killing of drug cartel leaders. These efforts led to reduced coca crops but unfortunately did not immediately affect the historically high cocaine production at the time – at the height of which approximately 1,000 metric tons were estimated to be produced each year. **One unforesseen result of this downward pressure on coca/cocaine was the novel introduction of poppy and heroin production – for the first time in Colombian history.** In a 2009 publication on this issue I stated; “The diversification of Colombian drug production and export to include heroin in addition to cocaine, with the resultant increase in heroin availability in the US, despite reduced supply from traditional sources, highlights a paradoxical effect of interdiction.”18 The influx of new Colombian-sourced heroin into the US led to a nationwide decrease in heroin price to historically low levels.19 The DEA’s metric for success in controlling a drug’s supply is increased price. Despite multi-decade efforts to control heroin into this country, whether from Afghanistan, Colombia or Mexico, heroin prices have remained at relative historically low levels.

**The under-recognized driver of drug mortality is demand and the under-treated root causes of drug demand.** A demand-side argument has been introduced examining the structural factors that might be driving the triple wave overdose epidemic.20 (Indeed they may be driving the 38-year exponential increase in overdose mortality.) The “diseases of despair” analyses highlight the extraordinary rise in death rates, among middle aged Whites without a college degree, in three related categories: drug poisoning, alcohol-related disease and suicide. The most compelling structural determinants include an aging population with rises in reported pain and disability, economic distress, declining social cohesion and rising psychological malaise that may have led an at-risk population to seek opioids in the first place [17]. In this line of reasoning increased opioid

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prescribing is a “vector” of the opioid overdose epidemic with more proximal root causes being worsening structural forces accompanied by generational hopelessness and despair [19].

The futility of fentanyl prohibition

The current issue is whether the emergency scheduling of fentanyl derivatives as a class in schedule 1 should be continued, perhaps permanently. There are a number of problems with a permanent class-wide fentanyl ban:

- The class of fentanyls has a large number of unexplored compounds, some of which are theoretically beneficial for treatment or as overdose antagonists. Schedule one classification will inhibit basic science and clinical research
- Emergency scheduling has not been shown effective in reducing fentanyl availability nor reduced the number of overdose deaths
- The ‘Iron Law’ of prohibition predicts stronger chemicals, more potent by volume, to be trafficked under greater supply control
- The high potency and low volume of fentanyl already strain the potential successfulness of interdiction. The supply control challenge is worsened by the move from agricultural-based to lab-based illicit drug manufacturing
- Making the class-ban on fentanyl permanent will likely increase trends in federal prosecution from fentanyl trafficking; countering the goals of public health as well as trends in sentencing reform for drug possession

More than 1400 fentanyl analogues have been synthesized as research chemicals and two hundred of these analogues have been studied pharmacologically.21 The DEA’s National Forensic Laboratory Information Service is actively tracking over 16 analogues which have entered the illegal drug market.22 The public health concerns center on the illicit fentanyl agonists which have abuse potential and overdose risk due to their potency, but research into fentanyls has identified potential antagonists, like naloxone, and partial agonists, like buprenorphine, which may be useful in treatment. Why is this important? Because of the potency of illicit fentanyl we need to explore new antagonists to reverse overdose and new treatments to address greater dependency. So we need better, perhaps stronger, perhaps longer lasting, antagonists and partial agonists – and they may come from the fentanyl class. This class ban will also potentially inhibit: 1, clinical trials of novel beneficial fentanyls and 2, clinical understandings of how fentanyls adversely affect health e.g. why overdose events are so severe.

It is important to note: as of the latest data, the currently active class-wide ban hasn’t yet shown effective. For example, my team and I have analyzed drug seizure data from the Ohio Bureau of Criminal Investigation's (BCI) crime lab from 2009 to 2018 (204,951 samples across 87 counties, providing 8,352 county-month observations) to examine trends and the relationship between drug seizures (type, amount) and overdose at the county level.16 Ohio has been exceptional hard-hit by the third wave – fentanyl – of the opioid crisis which began in 2014. Our analysis

shows the number of fentanyl analogues by year: The only fentanyl analogue detected in 2015 was acetyl fentanyl; eight new analogues appeared in 2016, six more appeared in 2017 and seven new analogues appeared in 2018. Other non-fentanyl synthetic opioids emerged as well: U-47700 in 2016 and U-48800, U-49900, and U-51754 in 2017. No decline in novel opioids over time was seen and the spill-over to non-fentanyl synthetics is concerning. However, it is important to note that the DEA class-wide scheduling took effect in Feb., 2018 so additional study is needed.

In a Commentary I published in the International Journal of Drug Policy, stemming from a testimony I gave in 2018 to a House subcommittee, I argued that synthetic opioids may represent the “end of interdiction.”23 One paradox of supply control that comes out of examining alcohol prohibition in 1920s America is termed the “Iron Law of Prohibition.” This ‘law’ predicts that drug weight and volumes go down while potencies go up due to supply control. During Prohibition the illicit alcohol trade shifted from beer to high alcohol content liquors to avoid detection. We see evidence of this effect in the current triple wave opioid crisis as supply pressures on opioid pills, esp. those illicitly marketed, shifted the street market to higher potency heroin to even higher potency fentanyl.14 The “Iron Law” suggests that highly potent-by-volume drugs like fentanyl are expected due to the honing effects of interdiction.24

Interdiction will be challenging given the size of illicit fentanyl flows. In 2016, a mere 668 kg of fentanyl was seized in the US, a fraction of the estimated 11 metric tons of cocaine seized in 2016 at the US Southwest Border alone. Fentanyl’s high potency allows shipment in small volumes. Considering a seizure to importation ratio of 1:4, a total of 2.6 metric tons of fentanyl may have been distributed in the US in 2016. This would fit into approximately 10 industrial drum barrels – a tiny volume that if divided up over the huge trade that occurs across the Pacific Rim constitutes a proverbial needle in a haystack.14

Why is it so hard to get the fentanyl supply genie back in the bottle? In their recent publication, The Future of Fentanyl, Bryce Pardo and colleagues discuss the drivers of the synthetic opioid market in the US: increased profitability, lack of regulatory capacity in the main source country, China, as well as technological advancements in purchasing (i.e. cryptocurrencies) and routing.25 The change in source-country of our imported illicit opioids is important: from known drug-producing countries, e.g. Afghanistan, Colombia and Mexico to new source-countries i.e. China. In addition, moving from agricultural based drugs, e.g. poppy and heroin, to lab-based drugs, e.g. fentanyl, makes the sourcing and routing more challenging to detect. The technology to produce fentanyl is mobile; if China were able to crack down on domestic production, the supply balloon could squeeze production to a novel source-country.

Making the class-ban on fentanyl permanent will likely increase trends in federal prosecution from fentanyl trafficking. Sentencing commission data show dramatic increases in fentanyl trafficking offenders, disproportionately among persons of color; with 41% having no prior criminal

25 https://www.rand.org/content/dam/rand/pubs/research_reports/RR3100/RR3117/RAND_RR3117.pdf
record and 50% at the bottom of distribution chain. The vast majority did not know they are selling fentanyl.26,27

Sociologists and anthropologists talk about “moral panics” when society collectively acts out of instinct or fear. This notion often fits when we respond to problematic drug waves. The moral panic over fentanyl leads to irrational claims and responses e.g. the fear that fentanyl cannot be touched or that fentanyl is being deliberately put into all substances, not just heroin. These myths are being debunked as we learn about fentanyl. We saw the same fear based reaction when HIV became epidemic in the 1990’s and folks with that disease were shunned and treated prejudicially. Fear, moral panic, penalization of drug use – all lead to stigma and marginalization of the affected population. And this is counter to the goals of public health which wants folks not to run and hide but to come forth for prevention and treatment services.

SUMMARY

- The third wave of the opioid overdose crisis continues to grow with increasing numbers of deaths in 2019 – despite the past two-year all-class fentanyl scheduling
- The class of fentanyl is very large with untapped research and clinical potential. Possible future therapeutic agents including antagonists and partial agonists are known to be present
- Fentanyl appears to be here to stay; illicit fentanyl represents a historic shift from agricultural based to lab-based illicit drug production – from an new illicit drug source country – China
- Users and low level dealers typically don’t know if the drug they’re selling/using contains fentanyl. Making the class-ban on fentanyl permanent will likely increase trends in federal prosecution from fentanyl trafficking which are disproportionately affecting those at the bottom of the supply chain
- The currently active class-wide ban has not yet shown effective examining data as of late 2018; the numbers of new fentanyl analogues – and non-fentanyl synthetic opioids e.g. the U-series – shows steady growth in hard-hit Ohio; more study is needed
- The “Iron Law” suggests that highly potent-by-volume drugs like fentanyl are expected due to the honing effects of interdiction
- Despite decades of strong prohibitionist efforts, drug mortality is increasing exponentially. The under-recognized driver of drug mortality is demand and the under-treated root causes of drug demand

Fear, moral panic and penalization of drug use – leading to stigma and marginalization of the affected population – run counter to the goals of public health

THE WAY FORWARD

I’ve lost too many colleagues, patients and research participants to overdose. I understand the desire to act, the need to do something to reduce the carnage. But I also know the danger of moral panic and the stigmatizing effects of excessively punitive approaches and exuberant supply reduction approaches. By increasing stigma – a very powerful force in human nature - they are simply counterproductive to the goals of public health.

Fentanyl is here to stay. They are the new norm. Instead of fear let us respond with a public health orientation of science, reason and compassion.

I have had the privilege to meet with criminal justice leaders, at various national meetings held by the National Institute of Justice, DEA, High Intensity Drug Trafficking Areas (HIDTAs) among others, and heard them state that “we are not going to arrest our way out of this.” They and leaders at the Office of National Drug Control Policy (ONDCP) have called for “public health / public safety partnerships. These shifts in political tone from leadership – and also the public – favor treatment over incarceration.

Chauncey Parker, Executive Assistant District Attorney in the Manhattan District Attorney’s Office and Director of the New York/New Jersey HIDTA program often speaks of his “North Star” in tackling the fentanyl problem: to reduce deaths. So what strategies are most likely to reduce deaths?

- Offer treatment over punishment. Pre-arrest diversion and other strategies to move folks from prosecution to medical help for their substance use disorder have a growing evidence base of effectiveness.
- Expand treatment for opioid use disorder. Medically assisted treatment (MAT) includes three medications shown to be medically effective and cost-effective. A recent meta-analysis showed impressive reductions in mortality attributable to receipt of MAT. Buprenorphine is one of the efficacious medications. It is esp. effective from a public health standpoint as it can be prescribed by primary care providers, e.g. family docs and nurse practitioners. However, regulatory burden, e.g. mandatory prescriber training and DEA licensing, inscribed in the DATA 2000 law authorizing its use has led to lower levels of prescriber uptake. The Mainstreaming Addiction Treatment Act of 2019, with House (H.R.2482) and Senate (S.2074) versions, attempts to address the barriers inherent in the original legislation.

• Increase federal funding. Federal legislative efforts to address the opioid crisis, e.g. Comprehensive Addiction and Recovery Act (CARA) and the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT) are quite helpful, yet much more is needed. Overdose deaths from all opioids have only fallen 2% since their peak in 2017.

• Greater support for prevention. Harm reduction ideas and prevention technologies, once controversial, are gaining both evidence and acceptance. Ideas such as syringe exchange are now supported by such leaders as Assistant Secretary Giroir at Health and Human Services and naloxone distribution, once quite controversial, has broad support including endorsement by the US Surgeon General Jerome Adams. HR’s goal is to reduce deaths and other harms from drug use; because it is person-centric it can reduce stigma and engage folks that use drugs; it can even serve as a bridge to treatment.

• Surveillance of the drug supply, a possible element of a public health / public safety partnership, can potentially act as an early warning system alerting front line responders to dangerous changes in supply.16 Another emerging novel approach includes drug checking. Heroin users who used fentanyl immunoassay test strips to check for fentanyl had greater odds of positive changes in behavior.31

At this moment we are, alas, still working on yesterday’s problem. **The 4th wave of the opioid crisis sees a shift in use patterns to methamphetamine and a dramatically rising curve in methamphetamine-related deaths. To end the multi-decade multi-generational exponential increase in drug mortality we need bold answers and creative novel responses.** There is growing evidence that we need to address the social, economic determinants of health – the root causes of the drug crisis – if we are to ‘fill in the cracks’ of society that the waves of drug supply fall into.19

Assisting Josh Katz at the New York Times, we surveyed 30 experts to “think big, but realistically, about solutions. Imagine you had $100 billion to spend over five years — a little less than current federal domestic H.I.V./AIDS spending — to address the opioid crisis. Where would you put that money?” The composite answer was a revelation: A comprehensive, but balanced plan including treatment, harm reduction, demand reduction and supply reduction.32 This schematic has been turned into policy platforms for a number of top political figures. Its implementation could signal the end of an unfortunate era.

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