The College on Problems of Drug Dependence

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"The Overdose Crisis: Interagency Proposal to Combat Illicit Fentanyl-Related Substances"

Testimony Submitted by

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Introduction

Chair, Ranking Member, and members of the Subcommittee, I am submitting this testimony to the Health Subcommittee of the House Energy and Commerce Committee for inclusion in the formal record of the Subcommittee Hearing "The Overdose Crisis: Interagency Proposal to Combat Illicit Fentanyl-Related Substances." I am Dr. Sandra Comer, the Public Policy Officer of the College on Problems of Drug Dependence (CPDD), a membership organization with over 1000 members that has been in existence since 1929. It is the longest standing organization in the United States (U.S.) and the world addressing problems of drug dependence and abuse. The organization serves as an interface among government, industry, and academic communities maintaining liaisons with regulatory and research agencies as well as educational, treatment, and prevention facilities in the field of substance use disorders (SUDs).

I am also a Professor of Neurobiology in the Department of Psychiatry at the Columbia University Irving Medical Center, and a Research Scientist at the New York State Psychiatric Institute. My research focus for nearly 3 decades has been on the development and testing of new approaches to the treatment of opioid use disorder (OUD).

Scope of the Problem

Approximately 31 million people worldwide have a substance use disorder related to controlled substances, but across all of the illicit drug classes, non-therapeutic use of opioids is associated with the most harm: 76% of deaths associated with SUDs have been attributed to opioids[1]. The U.S. in particular is experiencing an unprecedented increase in illicit use of opioids and its associated morbidity and mortality. During the 1-year period ending in April 2021, over 62,000 opioid-related overdose deaths were attributed to synthetic opioids such as fentanyl[2]. OD deaths are the tip of the iceberg as research suggests 20-30 non-fatal ODs occur for every OD death[3]. In addition, the majority of people who use opioids either have experienced a non-fatal OD or have witnessed an OD during their lifetime[4-6]. These numbers are likely to be underestimates because the data on non-fatal overdoses were collected prior to the introduction of illicitly manufactured fentanyl. ***Of great concern to the research community is that our tools for treating OUD and reversing opioid OD were developed before the emergence of highly potent illicit fentanyl so new approaches may be needed to address this challenge.***

Research Gaps

Fortunately, several medications are available and have been used successfully for treating OUD, including methadone, buprenorphine[7-9], and naltrexone[10-15]. Despite the clear clinical utility of these medications, approximately half of the patients who initiate medication relapse and/or drop out of treatment within 6 months[11,15,16]. Thus, there is a substantial need for improving the effectiveness of these medications, given the high relapse rates.

A number of preclinical studies have demonstrated that fentanyl is a highly potent opioid with a receptor pharmacology that differs from other opioids[17]. Multiple studies conducted in several different species have demonstrated that opioid agonist maintenance or irreversible antagonist administration was less effective in blocking the effects of higher efficacy agonists, like fentanyl, compared to intermediate efficacy agonists, like heroin or morphine[18-29]. ***Research on the ability of the approved medications for treating OUD in patients who are predominantly using fentanyl is clearly needed. The development of alternative medication approaches is also critically needed to address the shift in the illicit opioid supply toward fentanyl.***

Naloxone is a potent, short-acting medication that blocks opioid receptors. While it binds to opioid receptors, it does not activate them (that is, it doesn't produce a "high" or other desirable effect), so the risk of abusing the medication is non-existent. Naloxone is effective in both preventing and reversing the effects of heroin and other opioids, including respiratory depression, which is the primary cause of death due to opioid overdose[30]. The antagonist effects of naloxone are evident within 5 minutes following administration and its effectiveness at commonly prescribed doses (0.4-0.8 mg) can last 45 to 90 minutes. It is relatively ineffective orally, so it is typically administered intravenously or intramuscularly and more recently, intranasally[31-33]. Originally approved by the Food and Drug Administration (FDA) in 1971 for treating opioid overdose, naloxone is traditionally used in both emergency room and non-hospital settings, where it is administered by medically trained personnel.

Non-fatal and fatal opioid overdoses have increased substantially over recent decades. While provisional data suggest that the number of opioid overdoses has leveled off, they remain at alarming levels. Naloxone is now being used by individuals with little or no medical training in order to broaden our ability to address the opioid overdose crisis. Recent reports suggest that fentanyl and its analogues have contributed to the sharp increase overdose deaths and that higher and/or repeated dosing with naloxone may be required to reverse fentanyl-induced respiratory depression[34-36]. ***The reason that higher doses of naloxone may be required for fentanyl overdoses is not entirely clear.*** Possibilities are that a large dose of naloxone is needed simply because a large dose of fentanyl was used, a fentanyl analogue was used that is not sensitive to naloxone, or a post-receptor or non-opioid-receptor cascade of effects is initiated that is not sensitive to reversal by naloxone. Another possible explanation for the apparent lack of effectiveness of naloxone in some overdose situations is that fentanyl and naloxone may share a site that allows drug entry into the brain and when high doses of fentanyl are used, the ability of naloxone to pass into the brain is impeded[35,37]. Preclinical research suggests that other opioid antagonists may be more effective than naloxone in reversing fentanyl over-intoxication[38]. ***Clearly, additional studies are needed to understand the mechanisms by which fentanyl and its analogues produce severe respiratory depression. Furthermore, studies are needed to assess the effectiveness of naloxone and other opioid antagonists in reversing fentanyl-related OD because naloxone may not be the ideal compound for reversing the respiratory depressant effects of fentanyl-like drugs.***

The Need to Expand Research on Fentanyl-related Substances

The current fentanyl crisis poses a formidable challenge to Congress and the DEA since there are literally thousands of (existing or potential) fentanyl analogues, some of which have high abuse and dependence

potential. ***CPDD supports efforts to control the distribution, sales, and use of these synthetic fentanyls.*** In the face of the opioid crisis, it is critical that current restrictions imposed by licensing requirements for research on Schedule I compounds be streamlined while still preserving the Drug Enforcement Agency's ability to prevent against diversion of Schedule I compounds.

For a research scientist, obtaining a DEA Schedule 1 registration is complicated, burdensome, and can take a long time (e.g., more than a year), disincentivizing researchers in general and particularly young researchers (e.g., graduate students and postdoctoral fellows) who often need to complete their studies on strict academic schedules.

- The additional security that is necessary for handling Schedule 1 substances can be prohibitively expensive, particularly for young investigators in the current climate when securing NIH funding is very challenging. Specialized safes, locking refrigerators and freezers, video surveillance, and renovations can be expensive, and institutions often are not willing to pay these costs.
- Each additional Schedule 1 compound that might be of interest to study requires a protocol review that can take many months. Even for seasoned investigators who have been conducting research in this area for many years and who have efficient, well-funded laboratories, the delay in obtaining Schedule 1 compounds for experiments can be prohibitively long and significantly impedes progress. For example, one investigator reported that despite having a DEA Schedule 1 registration, importation from outside the U.S. of a Schedule 1 compound that proved to have significant therapeutic value and no abuse liability required nearly two years.
- Part of the difficulties in obtaining licenses to study Schedule 1 compounds stems from differing interpretations of registration requirements at both the state and federal levels, as well as at the academic administrative level.

Accordingly, CPDD strongly supports those provisions of the Administration Recommendations on Class-wide Scheduling of Fentanyl-Related Substances that streamlined current registration requirements for research on Fentanyl-related substances and all other Schedule I compounds. Those specific reforms, as outlined in Section 7 of the Administration's proposal and summarized in testimony provided by Dr. Nora Volkow[39] would legislate the following reforms to current Schedule I licensing requirements, including:

- Alternative Registration Process for Schedule I Research. The Administration's proposal would create a simplified process that would align Schedule I research registration more closely with the registration process for research on Schedule II substances. This new process would apply to research that is either (a) funded by the Department of Health and Human Services or the Veterans Administration, either intramurally or extramurally, or (b) done under an Investigational New Drug (IND) application exemption from the Food and Drug Administration that is in effect. Under this new proposed process, a Schedule II researcher would have to submit a notice to the Department of Justice containing the following information: the identity of the substance to be used in this research, the quantity of the substance to be used, demonstration that the above criterion is met, and demonstration that the researcher is allowed to do the research under the law of the state where the research will be done.
- Separate registrations would not be required for additional research in the same institution. Under current law, every individual using a Schedule I substance in research must have a registration to do so, with the exception of agents or employees of an individual who is

registered. This new provision would allow for individuals who are agents or employees of an institution but who are not technically the agents or employees of the individual who hold a Schedule I registration to perform research without being separately registered. This provision would be particularly helpful in the case of researchers who are part of a research team, but who are not necessarily agents or employees of the registrant. This provision would require the registered researcher to inform DOJ of the identities of all such individuals, would have to authorize them to participate, and would have to affirm that any acts involving controlled substances by such individuals would be attributed to the registered researchers for the purpose of determining whether the researcher should continue to be registered.

- Single registration for related research sites. Under this proposed revision, a single registration would cover use of multiple locations for performance of the research or storage of the substances, conditioned on those sites being under the control of the same institution and are in the same city or county, and the researcher notifying DOJ of each site before the site is used to conduct the research or store the substance. Current practice requires a separate registration for each principal location where the registrant works with Schedule I substances.
- New inspection not required in certain circumstances. This proposed revision would clarify that if a researcher has a registration to perform research with a controlled substance, and applies to research another substance controlled under the same schedule or under a less restrictive schedule, a new inspection of the research site is not required. However, this provision does not prevent DOJ from conducting any inspections deemed necessary to ensure that a registrant maintains effective controls against diversion.
- Continuation of research on substances newly added to Schedule I. Under this proposed revision, researchers with Schedule I registrations would be allowed to conduct research with newly added Schedule I substances on which they have been conducting research. Researchers would have to apply within 90 days for a registration (or modification of the existing registration) to work on the new substance, but research could continue uninterrupted until the application is withdrawn or until DOJ issues a show-cause order proposing to deny the application.
- Treatment of certain manufacturing activities as coincident to research. This proposed revision would clarify that a researcher would not be required to obtain a separate manufacturing registration if the manufactured quantities are small, if the manufacturing is done for purposes of the research, and if the researcher notifies DOJ of the manufacturing activities and the quantities of the substance that will be involved. This authority specifically includes creating different forms of the substance consistent with the research, and dosage form development studies performed in order to apply to FDA for an IND application exemption.

The proposed streamlining provisions outlined above, under this Administration's proposal, would apply to all Schedule I compounds, not just fentanyl-related substances.

Summary

We share the concerns of the Subcommittee about the opioid epidemic and its devastating consequence to millions of Americans, their families, and their communities. One of the main reasons for the dramatic and disturbing increase in illicit opioid use is the spread of fentanyl, a synthetic opioid

that is inexpensive and potent, as well as its analogues. The College supports robust, science-based efforts to curb the sale and use of synthetic analogues. CPDD supports efforts to give the DEA authority to control the importation and distribution of synthetic fentanyls, but we also believe that any legislation to address this issue should include language reducing some of the barriers to research currently imposed by Schedule 1 licensing requirements.

We thank you for considering our position on how these decisions may have a potentially negative impact on our shared efforts to address this serious public health issue.

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