U.S. House of Representatives
Committee on Energy and Commerce

"An Epidemic within a Pandemic: Understanding Substance Use and Misuse in America"

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Testimony submitted by

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Introduction

We share the concerns of the Committee about the opioid crisis and thank you for holding today's hearing on class-wide scheduling of synthetic fentanyls and for inviting me to provide this testimony. My name is Dr. Sandra Comer and I am 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 over 2 decades has been on the development and testing of new approaches to the treatment of opioid use disorder (OUD).

Scope of the Problem

Approximately 36 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: 80% of "healthy" lives lost as a consequence of disability and premature 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. In 2017, opioid overdoses (OD) claimed more than 47,000 lives in the U.S., more than 28,000 of which were attributed to synthetic opioids other than methadone[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.

The introduction of fentanyl and its analogues to the street supply of illicit opioids complicates an already difficult-to-treat disorder because it is not clear whether the approved treatment medications can reduce use of these drugs as effectively as they
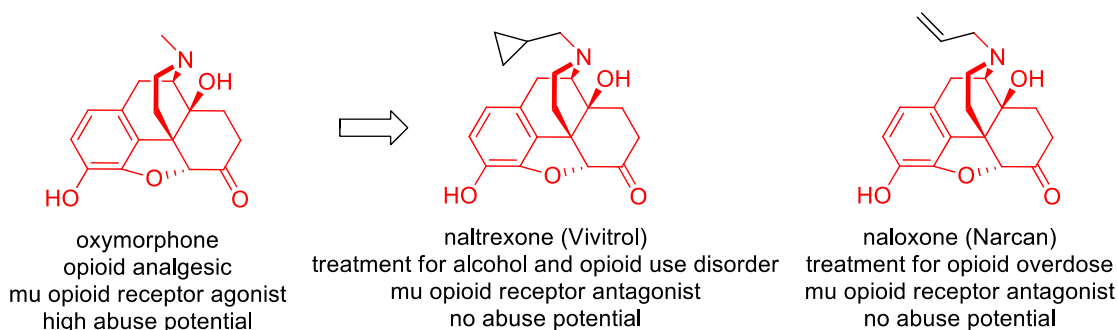
reduce the use of heroin and prescription opioids such as oxycodone. A number of preclinical studies have demonstrated that fentanyl is a highly potent opioid with a receptor pharmacology that differs from other opioids[17]. Multiple studies conducted in several different species have demonstrated that 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]. **Further 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. 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]. Emerging preclinical research suggests that naloxone may not be as effective against carfentanil, a highly potent fentanyl analog[38], and other opioid antagonists may be more effective than naloxone in reversing fentanyl over-intoxication[39]. **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.**
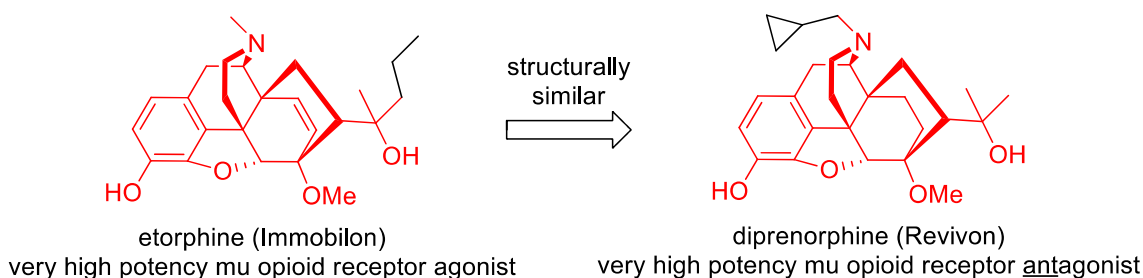
Class-wide Scheduling of Fentanyl Analogues from a Research Perspective

Fentanyl and related analogues are exceptionally potent, inexpensive, and easy to synthesize. Small modifications in these molecules can have profound effects on their activity, changing an inactive compound to a potent opioid with high abuse potential. ***A critical point is that similarity in chemical structure does not necessarily translate into similarity in abuse liability.*** Below is an example of how small modifications to a core chemical structure can result in large differences in pharmacological activity.

oxymorphone
opioid analgesic
mu opioid receptor agonist
high abuse potential

naltrexone (Vivitrol)
treatment for alcohol and opioid use disorder
mu opioid receptor antagonist
no abuse potential

naloxone (Narcan)
treatment for opioid overdose
mu opioid receptor antagonist
no abuse potential

Oxymorphone is a potent mu opioid receptor agonist with high abuse potential, while naltrexone and naloxone are opioid antagonists that have saved thousands of lives. Naltrexone is approved for treating both alcohol and opioid use disorder and naloxone is approved for treating opioid overdose. All three of these medications share the same core chemical structure (shown in red).

Another example of compounds that share similar structures but not pharmacological activity is etorphine and diprenorphine (below):

structurally similar

etorphine (Immobilon)
very high potency mu opioid receptor agonist

diprenorphine (Revivon)
very high potency mu opioid receptor antagonist

Etorphine is a very potent opioid used in veterinary medicine to tranquilize large animals and diprenorphine is an antagonist used as an antidote for etorphine. These examples illustrate how ***the antidote to a toxic substance and the toxic substance itself can share core chemical structures. However, the chemical structure of a compound alone cannot tell us whether it will have agonist or antagonist activity. Basic pharmacological studies must be performed in order to make this determination.***

- Science-based agencies, specifically the FDA and the National Institute on Drug Abuse (NIDA) at the Department of Health and Human Services (HHS), should review the pharmacological activity, not just the chemical structures, of these compounds.

- The role of HHS need not be as robust as the 8-factor analysis currently mandated by the Controlled Substances Act. Instead, ***the Committee should consider adding a role for HHS in subjecting compounds to more limited tests of pharmacological activity through animal models using a rapid process that could be undertaken by NIDA and a designated, pre-screened team of extramural scientists.*** In fact, NIDA, FDA, and the Drug Enforcement Administration (DEA) currently participate on the Interagency Committee for Drug Control, which reviews and prioritizes compounds that need analysis. NIDA issues grants and contracts for such analyses, as does the DEA.

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 tempting to globally put all compounds that are chemically similar to fentanyl in Schedule 1; however, such an action is likely to severely limit biomedical research and, in the long term, adversely impact public health. The opioid crisis is a very challenging public health issue and, arguably, we have yet to significantly turn the tide in this battle despite our current efforts. To restrict research by limiting access to potentially important compounds, based solely on chemical structure, is not likely to facilitate progress in this arena.

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 and those from small or historically Black colleges and universities that may not have the resources to comply with the regulations outlined in the Controlled Substances Act. 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 is 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.

Some suggestions for streamlining the process for obtaining a DEA registration to study fentanyl analogues are to:

1. Permit researchers holding a Schedule 2 license to conduct research on all Schedule 1 drugs. Specifically, treat the process for obtaining and modifying a Schedule 1 research registration the same as is currently in place for Schedule 2 (e.g., the DEA currently does not require FDA review of Schedule 2 substances for the purpose of obtaining a license.) NOTE: 1) FDA review will still be required for clinical studies of these substances during the Investigational New Drug application process, and 2) the security requirements are the same for Schedule 1 and 2 drugs so there are no implications for diversion.
2. Clarify that it is permissible for one individual to hold a Schedule 1 registration under which colleagues from the same institution may work even if those colleagues do not work directly for the registrant.
3. Eliminate the requirement to store each substance in a separate cabinet and for each individual researcher to have their own storage cabinet.
4. Allow registered researchers to store, administer, and otherwise work with any substances for which they hold a research registration at multiple practice sites on a single campus so long as the registrant notifies the Attorney General prior to conducting research at those sites.
5. Clarify that it is permissible for researchers to make limited modifications to the substances they are researching, such as processing them into extracts, solutions, or derivatives, without having to obtain a separate manufacturing license.
6. Allow individuals conducting research with a substance subsequently placed into Schedule 1 who hold a registration to conduct research with any other Schedule 1 or Schedule 2 substance to continue work on the newly scheduled substance until their new or amended registration application is approved or denied. These individuals will have to submit their new or amended registration application within 120 days of the substance being added to Schedule 1.

Investigators have dedicated their careers to research in this area because we want to make a difference in protecting individuals from the devastation caused by drug abuse. But we believe that more information, not less, is the most likely way we can achieve that goal. I encourage you and your colleagues to consider alternative approaches so that the potential benefits and risks of new chemical entities can be characterized before decisions are rendered regarding DEA scheduling.

Summary

We share the concerns of the Committee 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 and must address the unintended consequences of including such a broad range of substances in the scheduling language.

We strongly recommend that any legislation on scheduling synthetic opioids – either by extending the current temporary scheduling order, making permanent scheduling of these compounds, or requiring rapid tests of their pharmacological activity – should involve the Department of Health and Human Services' science-based agencies, specifically NIDA and the FDA.

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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