U.S. House of Representatives
Committee on the Judiciary
Subcommittee on Crime, Terrorism, and Homeland Security

"Fentanyl Analogues: Perspectives on Classwide Scheduling"

28 January 2020

Testimony Submitted by

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Introduction

Chair, Ranking Member, and members of the Subcommittee, thank you for holding today's hearing on classwide scheduling of synthetic fentanyls and for inviting me to testify. 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 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. 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

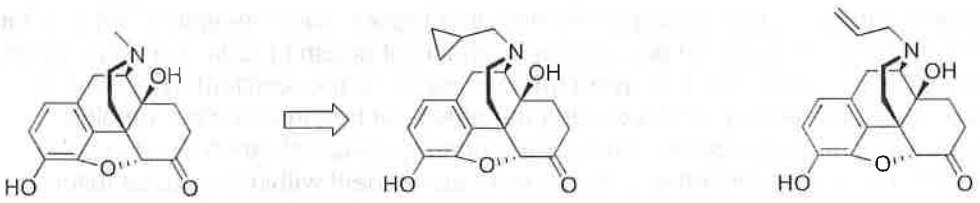
preclinical studies have demonstrated that fentanyl is a highly potent opioid with a receptor pharmacology that differs from other opioids[17]. Multiple studies conducted in several different species have demonstrated that opioid agonist maintenance or irreversible antagonist administration was less 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. 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]. Emerging 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.***

Classwide 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.



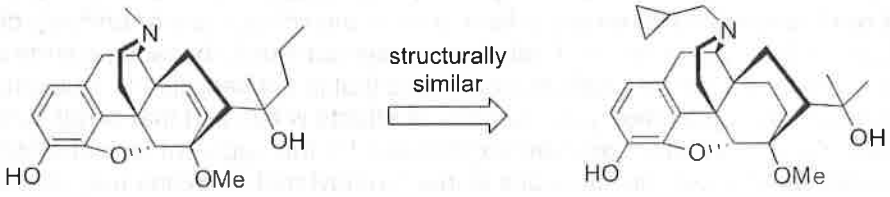
oxymorphone
opioid analgesic
mu opioid receptor agonist
high abuse potential

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):



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. 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:

- Require the Attorney General to register researchers unless it is not in the public interest, and further require researchers to submit their research protocols for review and approval by the Secretary of HHS, the National Institutes of Health, or pursuant to DEA's existing approval process. This streamlines the process compared to the current requirement for multi-agency approvals.
- Mandate that the Attorney General approve a complete application for Schedule 1 registration or request supplemental information within 60 days. If supplemental information is provided, the application must be granted or denied within 30 days of receipt. If the application is denied, the Attorney General must provide a written explanation.
- Permit researchers holding a Schedule 1 license to conduct research on all Schedule 1 drugs and allow a registrant to amend or supplement their research protocol without additional approvals required (subject to the next bullet).
- Expedite the process to make changes to the quantity, type, source, or conditions of storage, tracking, or administration of controlled substances. Require the registrant to submit an amended protocol to the Secretary and the Attorney General. Unless explicitly denied, the request is considered approved within 30 days of submission.
- Allow 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.
- Allow qualified research institutions and research laboratories to receive a blanket registration that would allow scientific investigators at the institution and laboratories to research Schedule 1 substances under a single license. The registrant will be required to notify DEA if it seeks to research a new Schedule 1 substance, and DEA to modify the registration appropriately. This allows qualified research institutions and research laboratories to engage in limited manufacturing of covered substances for research.
- Establish a 120-day grace period for newly designated Schedule 1 substances or analogues. If an applicant already has a registration to conduct research on a controlled substance, they may continue their research on the newly designated substance while waiting for their new application to be approved - while requiring researchers without an existing registration to submit one (as they continue to conduct their studies).
- Require that a practitioner, qualified research institution, or research laboratory to store Schedule 1 substances in securely locked, substantially constructed cabinets, eliminating the requirement to store each substance in a separate cabinet, other onerous cost-prohibitive measures, and arbitrary enforcement.
- Create a partnership between the Attorney General and members of the research community to expeditiously research newly discovered fentanyl-related substances.

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 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 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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APPENDICES

U.S. House of Representatives
Committee on the Judiciary
Subcommittee on Crime, Terrorism, and Homeland Security

"Fentanyl Analogues: Perspectives on Classwide Scheduling"

28 January 2020

How Regulating Fentanyl Structure Impacts Science

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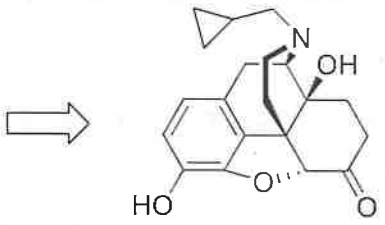
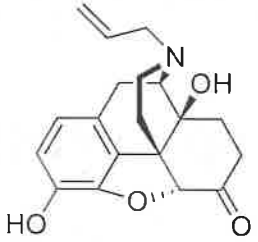
Blanket scheduling a class based on chemical structure is problematic: Very small changes to a chemical structure makes a potent agonist into an antagonist

oxymorphone
opioid analgesic
mu opioid receptor agonist
high abuse potential



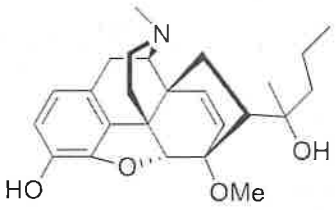
naltrexone (Vivitrol)
treatment for alcohol and opioid use disorder
mu opioid receptor antagonist
no abuse potential



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

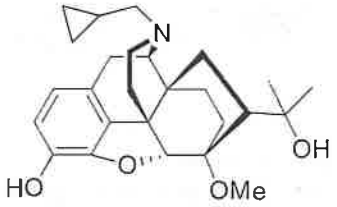
- Oxymorphone is an opioid receptor agonist with high abuse potential. The portion of the molecule shown in red is called a *4,5-epoxymorphinan*.
- Naltrexone (Vivitrol®) and naloxone (Narcan®) are also 4,5-epoxymorphinans (in red), but are opioid receptor antagonists that have saved millions of lives.

Blanket scheduling a class based on chemical structure is problematic

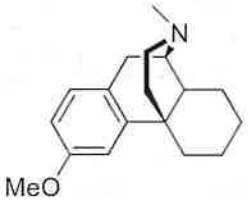


etorphine (Immobilon)
very high potency mu opioid receptor agonist

structurally similar

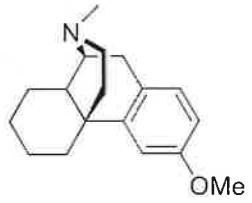


diprenorphine (Revivon)
very high potency mu opioid receptor antagonist



levomethorphan
mu opioid receptor agonist
analgesic

isomer



dextromethorphan (DXM)
NMDA antagonist
OTC cough suppressant
no opioid activity

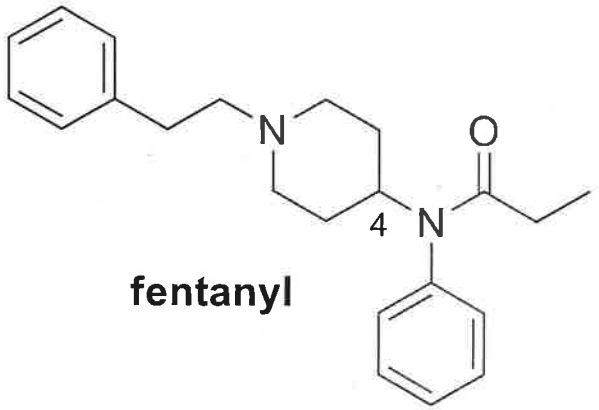
Compounds that have similar structures, or that are isomers, do not always share activity.

- Etorphine is a tranquilizer, whereas diprenorphine is its antidote.
- Levomethorphan is an analgesic, whereas DXM is an OTC cough suppressant.

Scheduling the isomer of levomethorphan would ban DXM.

Structure of fentanyl

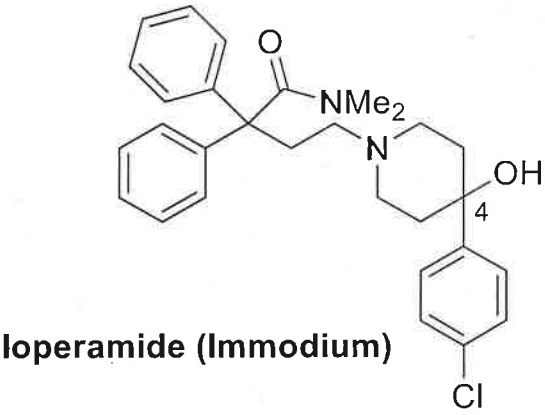
- Fentanyl is a 4-anilidopiperidine.
  - This group is shown in *red*.
- 4-Anilidopiperidine is not a common structural feature of current OTC medications or other pharmaceuticals.
- Piperidines with substitutions to the *N*- and 4-positions *are* common, however.



fentanyl

Will the proposed language identify other OTC or pharmaceutical products?

- Loperamide (Immodium®) is an anti-diarrheal.
- It *does not* have an anilide group at the 4-position of the piperidine.
- Like fentanyl, it *is* an agonist of the mu opioid receptor (MOPr).
- Unlike fentanyl, it *does not* get into the brain when taken as directed, so it has low abuse liability.

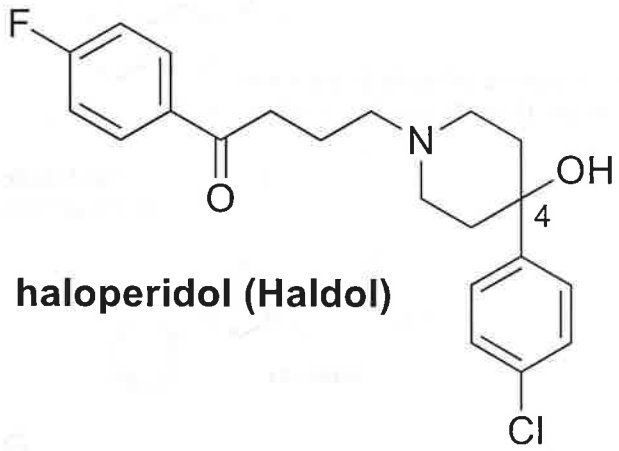


loperamide (Immodium)

Loperamide would not be covered under this language.

Will the proposed language identify other OTC or pharmaceutical products?

- Haloperidol (Haldol®) is an antipsychotic.
- It *does not* have an anilide group at the 4-position of the piperidine.
- Though its structure is very similar to loperamide, it has negligible affinity for MOPr.

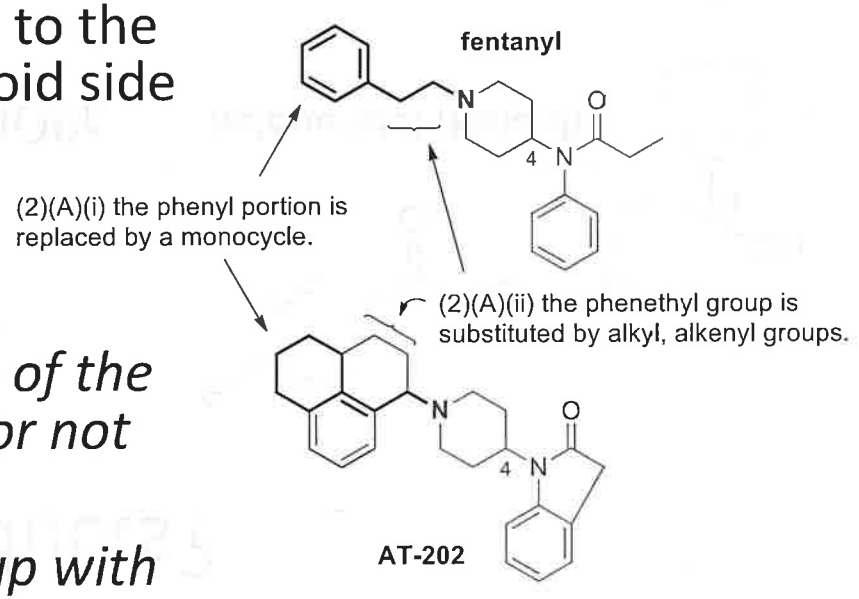


haloperidol (Haldol)

Haloperidol would not be covered under this language.

Will the proposed language cause problems for legitimate medication development?

- AT-202 is in development as an analgesic lacking abuse liability (Astraea Therapeutics). It contributed to the discovery of AT-121, which generates few opioid side effects in non-human primates.

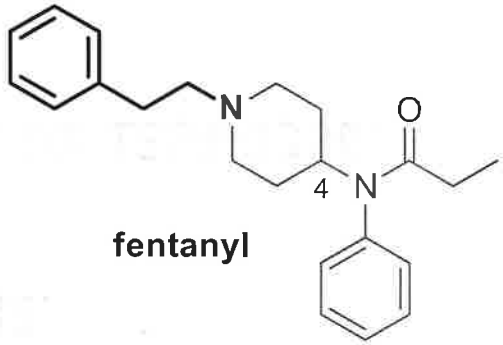


AT-202 <u>would</u> be covered under this language:

- *(2)(A)(i) By replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted on the monocycle.*
- *(ii) By substitution in or on the phenethyl group with alkyl, alkenyl, alkoxy, hydroxy, halo, haloalkyl, amino or nitro groups.*

Will the proposed language cause problems for legitimate medication development?

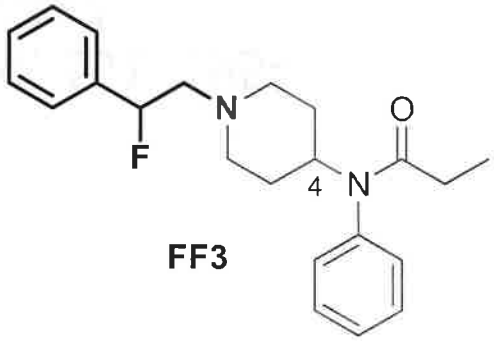
- FF3 was designed to selectively activate MOPr in inflamed tissues. Though opioid side effects were seen at high doses, this constitutes a potentially exciting new route to making safer analgesics.
- Dockendorff, et al., improved on FF3 (RR-49).



fentanyl

FF3 and RR-49 <u>would</u> be covered under this language:

- *(2)(A) (ii) By substitution in or on the phenethyl group with alkyl, alkenyl, alkoxy, hydroxy, halo, haloalkyl, amino or nitro groups.*



FF3

References

- Reviews: Cunningham et al., *Neuropharmacology*, 2019, 151: 195-207. Burns et al., *ACS Chem. Neurosci.*, 2018, 9: 2428-2437.
- AT-121: Ding et al., *Sci. Transl. Med.* 2018, 10: eaar3483.
- FF3: Spahn et al., *Sci. Rep.* 2018, 8: 8965.
- RR-49: Dockendorff et al., *ACS Med. Chem. Lett.* 2019, 10: 1353-1356.

THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, INC.

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Executive Officer: Loretta P. Finnegan, MD
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Director, Executive Office: Ellen B. Geller, MA

December 13, 2019

The Honorable Lindsey Graham
Chairman
U.S. Senate Committee on the Judiciary
224 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Dianne Feinstein
Ranking Member
U.S. Senate Committee on the Judiciary
152 Dirksen Senate Office Building
Washington, DC 20510

Re: Scheduling of Synthetic Opioids

Dear Chairman Graham and Ranking Member Feinstein:

On behalf of the College on Problems of Drug Dependence (CPDD) we are writing to express our concerns with any legislative proposals currently being considered by the Senate Judiciary Committee to add a large number of synthetic fentanyl compounds to Schedule 1 of the Controlled Substances Act either by extending the Temporary Emergency Scheduling of those compounds or to permanently add those compounds to Schedule I as proposed by the S. 1622, Stopping Overdoses of Fentanyl Analogues (SOFA) Act. The College has over 1,000 members, and serves as an interface among governmental, industry, and academic communities to maintain liaisons with regulatory and research agencies as well as educational, treatment, and prevention facilities in the drug abuse field.

We share the concerns of the Senate Judiciary Committee about the opioid epidemic and its devastating consequence to millions of Americans, their families, and their communities. According to the Centers for Disease Control, an estimated 28,466 Americans died in 2017 as a result of using synthetic opioids other than methadone. One of the main reasons for that dramatic and disturbing increase 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 Drug Enforcement Agency (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 I licensing requirements and must address the unintended consequences of including such a broad range of substances in the scheduling language.

The barriers to research imposed by Schedule I requirements could limit the ability of scientists to understand the pharmacology of these newer more powerful opioids and develop medications to treat use of and overdose on these substances. For example, the current language in the temporary emergency scheduling action of fentanyl analogues is broad and could result in an antidote, a fentanyl antagonist with no abuse liability, inadvertently being placed in Schedule 1. Any further broadening of the language describing fentanyl analogues could have even greater negative implications for development of therapeutically useful medications that have no opioid activity.

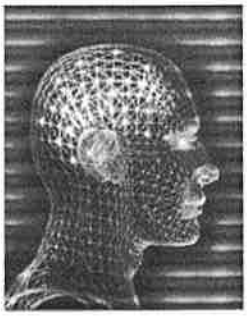
We strongly recommend that any legislation on scheduling synthetic opioids—either by extending the current temporary scheduling order or by making permanent scheduling of these compounds—should involve the Department of Health and Human Services' science-based agencies, specifically the National Institute on Drug Abuse and the Food and Drug Administration, in any decisions regarding scheduling of synthetic analogues.

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.

Respectfully,

Loretta P. Finnegan, M.D.
CPDD Executive Officer

Elise Weerts, Ph.D.
CPDD President



FRIENDS of NIDA

William L. Dewey
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July 25, 2019

The Honorable Lindsey Graham
Chairman
U.S. Senate Committee on the Judiciary
224 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Dianne Feinstein
Ranking Member
U.S. Senate Committee on the Judiciary
152 Dirksen Senate Office Building
Washington, DC 20510

Dear Chairman Graham and Ranking Member Feinstein,

On behalf of the Friends of NIDA we are writing to express our views on S.1622, Stopping Overdoses of Fentanyl Analogues (SOFA) Act. The Friends of NIDA represents hundreds of scientific organizations, service providers and patient advocate groups who collectively work to support funding for the National Institute on Drug Abuse and the application of that research to advance our understanding of the prevention, etiology and treatment of drug use, abuse and dependence.

We share the concerns of the Judiciary Committee and sponsors of S.1622 about the opioid epidemic and its devastating consequences for millions of Americans, their families, and their communities. According to the Centers for Disease Control, an estimated 28,466 Americans died in 2017 as a result of using synthetic opioids other than methadone. One of the main reasons for that dramatic and disturbing increase is the spread of fentanyl, a synthetic opioid that is inexpensive and potent, as well as its analogues. The Friends of NIDA support robust, science-based efforts to curb the sale and use of synthetic analogues.

The Friends of NIDA agree with the spirit of S.1622 but we are concerned about pending Senate Judiciary Committee action that would make the temporary emergency scheduling of synthetic fentanyl analogues permanent. We support efforts to give the Drug Enforcement Administration (DEA) authority to control the importation and distribution of synthetic fentanyl analogues, 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 we are concerned about the unintended negative consequences of including such a broad range of substances in the scheduling language.

The barriers to research imposed by Schedule 1 requirements could limit the ability of scientists to understand the pharmacology of these newer more powerful opioids and develop medications to treat use of and overdose on these substances. For example, the current language in the temporary emergency scheduling action of fentanyl analogues is broad and could result in a potential antidote to fentanyl overdose (e.g., a fentanyl antagonist with no abuse liability), inadvertently being placed in Schedule 1. Any further broadening of the language describing fentanyl analogues could have even greater negative implications for the development of therapeutically useful medications that have no opioid activity.

We strongly urge you to involve the National Institute on Drug Abuse and the Food and Drug Administration, in any decisions regarding scheduling of synthetic fentanyl analogues. We thank you for considering our position on these otherwise laudable efforts to address this serious public health issue. If you have any questions or need additional information, please contact Geoff Mumford, PhD, directly at gmumford@apa.org.

Sincerely,

American Academy of Addiction Psychiatry
American Academy of Neurology
American College of Neuropsychopharmacology
American Psychological Association
AMERSA
College on Problems of Drug Dependence
Friends of the National Institute on Alcohol Abuse and Alcoholism
Friends of the National Institute on Drug Abuse
National Alliance for Medication Assisted Recovery
National Families in Action
Treatment Communities of America