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RE: Comments on the SITSA Act

Our nation is facing an unprecedented epidemic of opioid abuse. Nevertheless, while I appreciate the attention Congress is giving to this issue, I am concerned that the SITSA Act will have unintended consequences for scientific research and drug discovery.

The SITSA Act allows substance to be controlled based on their structural similarity to controlled substances or their predicted pharmacological properties. Unfortunately, it is not always possible to reliably predict the pharmacological properties of new substances based solely on their structural features. Although structure-activity relationships have been defined for many drug classes, it is often the case that pharmacologists do not fully understand the molecular interactions between drugs and their biological targets, meaning that predictions about the pharmacology of novel substances must be confirmed empirically through experimental testing. Slight changes in the molecular structure of a drug can potentially markedly alter its pharmacological properties, often in unexpected or novel ways.

There are many controlled substance analogs that have been discovered to have unexpected, therapeutically useful pharmacological properties, demonstrating why it is necessary to confirm pharmacological predictions with biological testing. The following examples are illustrative:

(1) 3-Fluorofentanyl. It was recently reported in the journal *Science* that 3-fluorofentanyl is a potential non-addictive painkiller. Although 3-fluorofentanyl binds to the same primary target as the narcotic fentanyl — a protein known as the mu opioid receptor — it does so in a manner that restricts the interaction to injured tissues. Experimental testing indicates that 3-fluorofentanyl lacks abuse potential in rodents. Nevertheless, in the absence of experimental data, 3-fluorofentanyl and similar substances would likely be scheduled as controlled substance analogs under the regulations promulgated by the SITSA Act.

(2) UWA-101. UWA-101, a close structural analog of the Schedule I substance MDMA (Ecstasy), was recently developed as a potential treatment for Parkinson's disease. Testing has confirmed that UWA-101 does not produce MDMA-like effects in rodents, meaning that it is unlikely to have abuse potential in humans. Nevertheless, UWA-101 has pharmacological properties that are similar to those of MDMA, so the possibility exists that UWA-101 could be controlled as an MDMA analog under the SISTA Act. The case of UWA-101 is another example that shows why biological testing is necessary in order for the government to make accurate and informed scheduling decisions.

(3) Lisuride. Lisuride is a structural analog of LSD and these two drugs have virtually identical pharmacological properties. Nevertheless, lisuride does not produce hallucinogenic effects in humans and has actually been used in some countries as a treatment for Parkinson's disease and migraine. Although lisuride and LSD interact with the same primary target in the brain (the 5-HT_{2A} receptor), evidence indicates that they do so in subtly different ways, potentially explaining why lisuride does not produce hallucinogenic effects. Unfortunately, scientists are just beginning to understand how LSD interacts with the 5-HT_{2A} receptor and not enough is known about these interactions at the molecular level to reliably predict whether a new analog in this structural class will produce hallucinogenic effects or will mimic the effects of lisuride.

(4) BOL-148. Similar to lisuride, an analog of LSD known as BOL-148 (2-bromo-LSD) interacts with the 5-HT_{2A} receptor but does not produce hallucinogenic effects. Case reports published in the journal *Cephalagia* in 2010 indicate that BOL-148 may be an effective treatment for cluster headaches, which is an extremely debilitating medical condition.

(5) DOI. DOI is a structural analog of several hallucinogens regulated as Schedule I substances, including 4-methyl-2,5-dimethoxyamphetamine (DOM). According to recent reports in the scientific literature, DOI has potent anti-inflammatory effects, potentially making it a useful treatment for arthritis and asthma. The anti-inflammatory effects of DOI were discovered serendipitously — DOI happened to be available in the laboratory conducting this research and it was tested based on a hunch. At that time, there was no other evidence that DOI has anti-inflammatory effects and other chemicals in this class do not produce this effect. It is unlikely that this effect of DOI would have been discovered if it had been scheduled as a controlled substance analog.

(6) Loperamide. The anti-diarrheal loperamide, which is marketed over the counter in the USA under the brand name Imodium™, is an analog of diphenoxylate (a Schedule II narcotic) and diphenoxin (a Schedule I narcotic). Loperamide is a potent agonist at the mu opioid receptor but has little abuse potential because it is actively removed from the brain by a transport protein. Loperamide is yet another example that shows how structural features are not always a reliable predictor of abuse potential.

I am concerned about the repercussions of loosening the criteria for scheduling analogs of controlled substances. To date, several substances that have undergone emergency scheduling were later determined to have no abuse potential. Examples include benzylfentanyl and thenylfentanyl, which were emergency scheduled by the DEA in November 1985, and trifluoromethylphenylpiperazine, which was emergency scheduled in September 2002. Although such erroneous emergency scheduling actions have been rare, the changes to the CSA proposed in the SITSA Act will greatly increase the likelihood that substances lacking abuse potential are erroneously scheduled.

Unfortunately, erroneous scheduling actions have detrimental consequences for science and medicine. Scheduling all compounds that are even remotely related to drugs of abuse as controlled substance analogs will hinder promising research efforts to discover new therapeutic agents. Furthermore, many important “tool compounds” that are routinely used by scientific researchers to study drug responses are structurally related to controlled substances. Although these compounds lack abuse potential, I fear that the availability and use of many of these important tools will be restricted under the regulatory regime proposed in the SITSA Act. The SITSA Act does contain a research exemption, but it does not make sense, in my opinion, to place restrictions on research with these substances unless they actually have abuse potential.

Another aspect of the SITSA Act that would likely harm scientific research is the provision requiring researchers to register as manufacturers in order to distribute Schedule A compounds for use by collaborators at other research institutions. Currently, Schedule 1 researchers are not required to register as manufacturers in order to distribute these substances to collaborators who are licensed by the DEA to work with the same substances. Under the CSA, manufacturers have very burdensome security requirements because they often work with substances in bulk quantities; by contrast, it is not practical for researchers to register as manufacturers in order to synthesize and distribute small quantities of scheduled substances to collaborators. This particular regulation would likely limit the availability of Schedule A substances for research. Although some researchers will be able to synthesize the substances themselves or obtain them from colleagues at the same institution, neither of those options will be feasible for most investigators.

In summary, I am concerned that legitimate research will be hindered by scheduling all compounds that are structurally related to drugs of abuse. Furthermore, it is not clear that new legislation is necessary in light of the recent emergency scheduling action by the DEA to control an entire structural class of fentanyl analogs. Thank you for considering my thoughts on this important issue. If you would like to discuss this matter further, please feel free to contact me.

Sincerely,

Adam L. Halberstadt, Ph.D.