Potential unintended consequences of class-wide drug scheduling based on chemical structure: A cautionary tale for fentanyl-related compounds

ABSTRACT

Illicitly manufactured fentanyl and its analogs (i.e., fentanyl-related compounds) have flooded the street drug market in recent years and the continuing rise in opioid-related overdose deaths in the United States (U.S.) is now attributed primarily to these compounds. In response to this crisis, the U.S. Drug Enforcement Administration (DEA) enacted a 2-year emergency class-wide ban on fentanyl-related compounds by temporarily placing them into Schedule I of the Controlled Substances Act, meaning that these compounds have high abuse potential but no approved therapeutic use (Docket No. DEA-476 21 CFR Part 1308; Federal Register Vol 83, No. 25, February 6, 2018). The initial temporary class-wide scheduling of fentanyl-related compounds was re-authorized on February 6, 2020 and will remain in effect until May 6, 2021. While this action is understandable from a law enforcement perspective because it theoretically will make it easier to prosecute those who illicitly manufacture these substances, it is likely to have several unintended consequences from a scientific and medical perspective that may hamper our ability to combat the opioid crisis in the long run. The current paper describes these unintended consequences. The main problem with class-wide bans is that potentially thousands of compounds are defined solely by their chemical structures without regard for their pharmacological activity. As such, an antagonist (i.e., a medication that could be used to reverse an overdose but would not produce a drug “high”) could be mistakenly included in the class-wide ban. Another unintended consequence of a class-wide ban on synthetic fentanyl-like compounds is that the regulatory burden may complicate the development of novel medical interventions such as vaccines and monoclonal antibodies for treating opioid use disorders (OUD) and preventing fentanyl-related overdoses. There is much that we do not understand about how to most effectively treat fentanyl-related overdoses and OUD so any regulatory effort hindering research in this area will be counter-productive in the long term.

1. Introduction

Approximately 36 million people worldwide suffer from a substance use disorder (SUD), but across all of the drug classes, non-therapeutic (i.e., recreational) use of opioids is associated with the most harm: 80% of “healthy” lives lost as a consequence of disability and premature death related to SUDs have been attributed to opioids (World Drug Report, 2020). The United States (U.S.) in particular is experiencing an unprecedented increase in illicit use of opioids and its associated morbidity and mortality. During the 12-month period ending in May 2020, over 81,000 drug overdose (OD) deaths occurred in the U.S., which is “the largest number of drug overdoses for a 12-month period ever recorded” (Network, 2020). These deaths were driven primarily by illicitly manufactured fentanyl. It has been estimated that at least 50% of fatal ODs involve fentanyl, which is often encountered as a standalone product, an adulterant in heroin, or an ingredient in counterfeit pain medications (Jannetto et al., 2019; Han et al., 2019). Fentanyl is a prescribed medication, used for both anesthesia and analgesia, that acts as a µopioid receptor (µOR) agonist and is 50- to 100-times more potent than morphine. Fentanyl encountered in recreational drug markets is not a diverted pharmaceutical product, rather it is illicitly manufactured and trafficked over the Internet and by other channels. Of great concern to the medical research community is that our tools for treating opioid use disorder (OUD) and reversing opioid OD were developed before the emergence of highly potent illicitly manufactured fentanyl in the recreational drug market, so new approaches may be needed to address this challenge.

2. Medication development challenges

Several medications are available and have been used successfully for treating OUD, including methadone, buprenorphine (Ling and Wesson, 2003; Johnson et al., 1992, Johnson et al., 2000), and naltrexone (Comer et al., 2006; Krupitsky et al., 2011, Krupitsky et al., 2012, Krupitsky et al., 2013; DeFulio et al., 2012; Everly et al., 2011). Despite the clear clinical utility of these medications, approximately half
of the patients who initiate medication will relapse and/or drop out of treatment within 6 months (Krupitsky et al., 2012; DeFulio et al., 2012; Soya et al., 2008). Thus, there is a substantial need for improving the effectiveness of these medications, given the high relapse rates.

The introduction of fentanyl and its analogs (i.e., fentanyl-related compounds) 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 in some ways from other opioids (Torravala et al., 2020; Torravala and Janowsky, 2019; Comer and Cahill, 2019). Multiple studies conducted in different species have demonstrated that opioid agonist maintenance or irreversible antagonist administration is less effective in blocking the effects of higher efficacy agonists, like fentanyl, compared to intermediate efficacy agonists, like heroin or morphine (Walker and Young, 2001, 2002; Winger and Woods, 2001; Barrett et al., 2001; Walker et al., 1995, 1998; Smith and Picker, 1998; Pitts et al., 1998; Duttaroy and Yoburn, 1995; Paronis and Holtzman, 1992, Paronis and Holtzman, 1994; Young et al., 1991). In addition, recent pharmacokinetic studies suggest that fentanyl clearance is slower than other opioids (Huhn et al., 2020), and withdrawal symptoms following discontinuation of fentanyl use are more severe when compared to heroin and other prescription opioids (Neimark, 2020), which may necessitate new strategies for transitioning patients with OUD onto buprenorphine or naltrexone. Further research is clearly needed to assess the utility of approved medications for treating OUD in patients who are predominately using fentanyl. The development of new medications and treatment approaches is also critically needed to address the shift in the illicit opioid supply toward fentanyl.

In addition to investigating novel approaches for treating OUD in patients predominantly using fentanyl, new strategies for reversing fentanyl-related ODs are also critically needed. Naloxone is a potent, short-acting medication that blocks opioid receptors, including μORs, which are involved in both therapeutic and adverse effects of opioids. Naloxone was first approved by the Food and Drug Administration (FDA) in 1971 for treating opioid OD, where it is used in both emergency rooms and outside of hospitals by medically trained personnel to reverse opioid-induced respiratory depression, which is the primary cause of death due to opioid OD (White and Irvine, 1999). While naloxone binds to ORs, it does not activate them (i.e., it acts as a receptor antagonist) and does not produce any subjective “high” or other desirable effect from a drug user’s perspective, so the risk of ilecting using naloxone itself is non-existent. The antagonist effects of naloxone are evident within 5 minutes after administration and its effectiveness at commonly prescribed doses can last 45 to 90 minutes. It is relatively ineffective orally, so it is typically administered intravenously or intramuscularly and more recently, intranasally (Merlin et al., 2010; Kerr et al., 2009; Kelly et al., 2005). It is important to note that naloxone administration to opioid-dependent patients can induce withdrawal symptoms, which can be severe (Neale et al., 2020).

Non-fatal and fatal opioid ODs have increased substantially over the past three decades. While provisional data suggest that the number of opioid ODs started to level off in 2019, they are again increasing, as noted above, and remain at alarming levels. It has been estimated that since the beginning of the COVID-19 pandemic due to the novel coronavirus (CoV-2) pandemic, 10% of the nation’s opioid users (https://www.odmap.org/Content/Docs/news/2020/ODMAP-Report-June-20.pdf), and that fatal synthetic opioid-related ODs increased more than 50% in 18 of 38 jurisdictions (Network, 2020). Naloxone is now being used by individuals with little or no medical training in order to broaden our ability to reduce opioid-related OD deaths. However, some reports suggest that repeated dosing with naloxone may be required to reverse fentanyl-induced respiratory depression (Raza Lynn and Galinkin, 2018; Somerville et al., 2017; Fairbairn et al., 2017). The reason why higher doses of naloxone may be required to reverse fentanyl ODs is not entirely clear. It is possible that more naloxone is needed simply because a large dose of fentanyl was used, a fentanyl analog that is not sensitive to naloxone was used, or a post-receptor or non-opioid-receptor cascade of effects was initiated that is not sensitive to reversal by naloxone. Another possible explanation for the apparent lack of effectiveness of naloxone in some OD situations is that fentanyl and naloxone may share a common site of drug entry into the brain and when high doses of fentanyl are used, the ability of naloxone to pass into the brain is impeded (Raza Lynn and Galinkin, 2018; Suzuki et al., 2010). Emerging preclinical research suggests that other opioid antagonists, such as diprenorphine or nalufenine, may be more effective than naloxone in reversing fentanyl intoxication and OD (Krieter et al., 2019; Hill et al., 2019). Finally, another possibility is that naloxone was not properly administered in OD scenarios involving untrained bystanders, although a recent study suggests that non-medical bystanders who receive training in how to recognize an opioid OD and administer naloxone are proficient at using naloxone to reverse an opioid OD (Neale et al., 2019). Clearly, additional studies are needed to understand the mechanisms by which fentanyl and its analogs produce severe respiratory depression. Furthermore, studies are needed to assess the effectiveness of other opioid antagonists in reversing fentanyl-related OD because naloxone may not be the ideal compound for reversing the respiratory depressant effects of fentanyl-related compounds.

3. Class-wide banning of fentanyl-related compounds

The current fentanyl crisis poses a formidable challenge to Congress and the DEA since there are thousands of (existing or potential) fentanyl analogs, some of which have high abuse liability and dependence potential. While fentanyl, sufentanil, alfentanil, remifentanil, and other fentanyl-related prescription opioids are classified as Schedule II, more potent and toxic analogs with no therapeutic value are classified as Schedule I. Carfentanil represents an intriguing example of a highly potent opioid that is classified as Schedule II because it is used in veterinary medicine to immobilize large animals. Radiolabeled carfentanil is also used in trace amounts as a positron emission tomography (PET) imaging agent to label μORs. Importantly, the use of carfentanil has been increasingly regulated due to concerns for its potential use in chemical attacks or mass casualty scenarios. Because fentanyl analogs are classified as either Schedule I or II controlled substances, it is challenging to balance their clinical use and their improper recreational use from a regulatory standpoint. In the face of the opioid crisis, it seems tempting to legally ban all compounds that are chemically similar to fentanyl. Indeed, the U.S. DEA enacted an emergency class-wide ban on fentanyl-related compounds in 2018 by temporarily placing them into Schedule I (Docket No. DEA-476 21 CFR Part 1308; Federal Register Vol 83, No. 25, February 6, 2018). As defined by this temporary order, “fentanyl-related substances include any substance not otherwise controlled in any schedule (i.e., not included under any other Administration Controlled Substance Code Number) that is structurally related to fentanyl by one or more of the following modifications:

(A) Replacement of the phenyl portion of the phenethyn group by any monocyte, whether or not further substituted in or on the monocyte;
(B) substitution in or on the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;
(C) substitution in or on the piperidine ring with alkyl, alkenyl, alkoxyl, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;
(D) replacement of the aniline ring with any aromatic monocyte whether or not further substituted in or on the aromatic monocyte; and/or
(E) replacement of the N-propionyl group by another acyl group.”
Unfortunately, class-wide banning based on chemical structure is likely to have unintended consequences including severely limiting biomedical research and, in the long term, adversely impacting 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.

The following sections highlight the challenges associated with class-wide scheduling based on chemical structure without accounting for empirically determined pharmacologic activity in vivo. Examples are provided that demonstrate limitations in predicting abuse liability from structure-activity relationships (SAR) or chemical structural similarity, instances where potentially non-addictive analgesics and therapeutics are mistakenly covered under broad regulatory language, and implications for class-wide scheduling disrupting the development of small molecules and biologics against OUD and overdose.

4. Opioid SAR and abuse liability must be determined empirically

Opioids produce their effects through several subtypes of receptors, including mu, kappa, and delta opioid receptors (μORs, κORs, and δORs) and nociceptin-orphanin FQ peptide (NOP) receptors, each of which produces a unique profile of pharmacological responses. Morphine and codeine contain a rigid 4,5-epoxymorphinan structural skeleton that has been the subject of comprehensive SAR studies for many decades (Casy and Parfitt, 1986). Though some trends are generally observed within a congeneric series – such as N-methyl-substituted 4,5-epoxymorphinans being high-efficacy μOR agonists – these trends should not be taken as absolute fact across structurally related, non-congeneric series. Recent examples of exceptions to the expected SAR of epoxymorphinans are shown in Fig. 1. One example is benzylidenemorphine (BOM, compound 1), a 4,5-epoxymorphinan that shares the pharmacophore and N-methyl substitution pattern of oxymorphone, a potent μOR agonist. In contrast to the general trend that N-methyl-substituted derivatives are high-efficacy μOR agonists, 1 is a low-efficacy (Emax < 50%) μOR partial agonist that was empirically determined to have very low abuse liability in preclinical tests of motivated behavior (Mada et al., 2020; Healy et al., 2017). In another example, Husbands and colleagues (Ding et al., 2016) described the design of an orvinol analog of buprenorphine (Fig. 1, compound 2, defined below as BU08028) whose chemical structure differs from buprenorphine by the addition of a single methyl group. Crucially, this simple structural change imparts substantial changes in its receptor binding profile that introduces NOP receptor binding affinity and efficacy, in addition to activity at μORs. Preclinical assessment of BU08028 (compound 2, Fig. 1) in non-human primates demonstrated antinoceceptive and antiallodynic effects without the associated adverse effects that limit traditional μOR agonists: abuse liability, physical dependence, and respiratory depression were all significantly reduced for BU08028 when compared to morphine (Ding et al., 2016). The examples of BOM and BU08028 highlight the challenge in drawing broad conclusions about abuse liability of opioids based purely on SAR trends without accounting for in vivo pharmacologic activity.

5. Potentially problematic outcomes of scheduling 4-anilidopiperidines based on structure

Fentanyl is a member of the 4-anilidopiperidine structural class that was developed by Janssen Pharmaceuticals in 1972 (Burns et al., 2018). The ease of synthesis of 4-anilidopiperidines and their structural analogs was an advantage in early drug discovery efforts because large libraries could be generated (Scheme 1), and their opioid receptor SAR could be evaluated quickly using in vitro methods and in vivo analgesic testing. The SAR for 4-anilidopiperidines have been reviewed (Vardanyan and Hruby, 2014; Vuckovic et al., 2009). The reagents required to synthesize these analogs are generally inexpensive and widely available. Thus, the ease in synthesis and availability of precursor reagents has fueled the proliferation of dozens of analogs of fentanyl generated by clandestine laboratories; however, these attributes, when combined with the relatively simple structure of 4-anilidopiperidines, are also advantageous during the development of diverse classes of therapeutics. As with 4,5-epoxymorphinans, scheduling 4-anilidopiperidines based on the chemical structure and SAR alone has the potential to capture compounds lacking significant potential for harm while also missing compounds that have documented abuse liability. This would have a negative effect on innovation, particularly in terms of developing safer analgesics or other medical interventions that incorporate small molecule-based components. A non-exhaustive list of fentanyl derivatives that would fail in this category is shown in Fig. 2 and discussed below.

Whereas the rewarding effects of opioids that contribute to SUDs are mediated primarily through activation of mesolimbic μORs, consider-able evidence implicates μORs in both the central and peripheral nervous systems as contributing significantly to analgesic effects. Consequently, peripherally restricted μOR agonists could be viable as analgesics with reduced abuse potential and propensity for physical dependence. This is exemplified by compound 3. The rationale behind the design of 3 is that long-chain polyethyleneglycol (PEG) ethers add molecular size and polar surface area, two properties that limit passive permeability across the blood-brain barrier (BBB) (Averick SB et al., 2017).

Another innovative approach to peripheral drug development takes advantage of pH differences in inflamed vs. non-inflamed tissues. Strategic addition of fluorine to either the piperidine ring or N-arylalkyl substituent lowers the pKa of the basic amine. As a protonated amine is a requirement for fentanyl binding to μORs, compounds like 4 and 5 have highest μOR affinity in inflamed tissues where pH is below 7.42,53. Though evaluation of the behavioral effects of these compounds remains limited, robust preclinical development of this concept would be severely impacted by class-wide banning of fentanyl-related compounds.

In some cases, the abuse liabilities of fentanyl analogs have been empirically determined to be low. Mirfentanil (6) is an example of a fentanyl analog with a unique pharmacodynamic (PD) profile that is...
incompletely understood. Preclinical in vivo evaluation suggests that this compound possesses a multimodal mechanism of action and also has low abuse liability (France et al., 1995). Despite the fact that preclinical evaluation of mirfentanil suggests low abuse liability, its structural similarity to fentanyl would cause this candidate to be improperly categorized under Schedule I, despite having low documented potential to cause harm.

4-Anilidopiperidines have affinity for alternate targets and can be developed for diverse pharmacologic outcomes. For example, AT-202 (7) was developed as part of a robust analgesic development program by Astraea Therapeutics. Different from other µOR agonists, AT-202 and related compounds have high affinity for the NOP receptor (Toll et al., 2009). The NOP receptor emerged as a viable target for analgesic development that does not share the adverse effects profile of µORs. In vivo evaluation of the related compound, AT-121, showed potent antinociception in non-human primates, with negligible abuse liability. Other, non-opioid compounds that would satisfy the criteria outlined in the temporary scheduling order include 8 (glycine transporter inhibitor (Alberati-Giani et al., 2004)), 9 (anti-inflammatory (Ghosh et al., 2004)), 10 (anti-allergy (Ozawa MS et al., 2008)), and 11 (HIV attachment inhibitor (Wang TY et al., 2014)). The inclusion of these latter two compounds as possibly targeted under the temporary scheduling order is considered questionable: though carbonyl substitution is not expressly included under the criteria listed, other oxidation states, e.g., hydroxyl and methoxy, are included.

The language in the temporary scheduling order misses close structural classes of fentanyl analogs that can be exploited (Fig. 3). One example is the short-acting anesthetic, remifentanil (Ultiva). In order to be classified as a fentanyl analog under the temporary scheduling order, remifentanil must have a monocyclic group attached to the basic amine; instead, this group is replaced by a methyl ester. The N-phenethyl portion of fentanyl is tolerant of diverse structural modifications and is likely able to be modified to avoid inclusion under this order.

Another concern is the tolerance of the aniline portion to homologation and modification. Casey and Huckstep reported in 1988 that the N-4-benzyl (12) and N-4-phenethyl (13) amide analogs are approximately equipotent with morphine in the warm-water tail-withdrawal test in rats (Casey and Huckstep, 1988). Of note, the N-1-phenethyl group of 12 could be replaced with an N-1-methyl (14) and maintain potent antinociception in this test. This is particularly problematic, since clandestine
6. Barriers to the development of vaccines and antibodies against fentanyl or its analogs

Classification of fentanyl derivatives or analogs into either Schedule I or II may have an impact beyond development of small molecule-based medications and their clinical implementation. Opioid-based small molecules are used as key components to generate either conjugate vaccines or isolate monoclonal antibodies (mAbs) to treat or prevent Opioid Use Disorder (OUD and opioid-related fatal ODs) (Baehr et al., 2020; Pravetoni and Comer, 2019). Vaccines consist of opioid-based small molecule haptens conjugated to higher molecular weight immunogenic carriers (e.g., bacterial or viral proteins, nanoparticles), and formulated in adjuvant or other platforms (e.g., liposomes) to improve immunogenicity and delivery (Fig. 4, panel A). Active immunization with vaccines stimulates the innate and adaptive immune system over time to generate polyclonal antibodies specific for the target opioid (Pravetoni, 2016). In contrast, passive immunization with mAbs provides almost immediate therapeutic levels of antibodies. Upon drug consumption, either polyclonal antibodies or mAbs will selectively bind the target drug preventing its distribution across the BBB, and decreasing its pharmacological, physiological, and behavioral effects. Pre-clinical studies have shown that vaccines and mAbs are effective in reducing fentanyl-induced antinociception, respiratory depression, bradycardia, and fentanyl self-administration in various animal models (Baehr et al., 2020; Raleigh et al., 2019; Tenney et al., 2019; Bremer et al., 2016; Smith et al., 2019; Robinson et al., 2020; Barrientos et al., 2020). Pre-clinical efficacy for these emerging immunotherapeutic interventions also extends to sufentanil, carfentanil, and other Schedule I or Schedule II fentanyl analogs (Bremer et al., 2016; Smith et al., 2019; Robinson et al., 2020; Barrientos et al., 2020). Because of their selectivity, vaccines and mAbs do not interfere with the pharmacological activity of naloxone, naltrexone, methadone, buprenorphine, and other opioid agonists used in pain management or anesthetics used in critical care (Baehr et al., 2020; Raleigh et al., 2019; Tenney et al., 2019; Bremer et al., 2016; Smith et al., 2019; Robinson et al., 2020; Barrientos et al., 2020).

Despite their promising pre-clinical proof of efficacy, selectivity and safety, one of the major challenges in translation of vaccines for OUD remains their manufacturing under Good Manufacturing Practice (GMP) to support preclinical and clinical evaluation. Our experience relates to development of vaccines targeting oxycodone, heroin, and fentanyl (Fig. 4). Specifically, in order to synthesize opioid-based haptens, perform their conjugation to carrier proteins, and formulate these conjugates in adjuvant or other vehicle, our team engaged contract development and manufacturing organizations (CDMOs) and contract manufacturing organizations (CMOs) capable of performing such tasks under GMP. Hence, the biggest regulatory challenges were to first clarify the hapten status through its chemical evaluation by the DEA, and then to acquire appropriate regulatory approval to conduct such work.

Haptens derived from the morphinan structures consisting of either oxycodone or morphine derivatized at the C6 position and equipped...
with a tetracyclic linker [(Gly)$_4$ (Pravetoni et al., 2012a, 2012b)] were classified by the DEA as Schedule II (Fig. 4, panel D and E), despite lacking activity at μORs in vitro (data not shown). For instance, both the OXY(Gly)$_4$ hapten and its intermediate oxycodeone-(6-norketoxo-(2-ideneamino)oxy)acetic acid were defined as Schedule II according to the 21 United States Code 812(a)(1) Schedule II and 21 CFR 1309.12(b)(1) because they retain chemical structures characteristic of the oxycodeone parent compound. In contrast, the analogous fentanyl-based hapten F(Gly)$_4$ was not classified as a controlled substance under the Title 21 Code 1308.11(h)(30) because it does not contain the N-phenylethyl moiety, which is a structural feature critical for agonist activity at μORs (Fig. 4, panel C and F), as confirmed by F(Gly)$_4$'s lack of activity at μORs in in silico and in vitro assays (Robinson et al., 2020). While none of these opioid-based haptens [OXY, M, and F] displayed functional agonist activity at μORs, only the F(Gly)$_4$ was ruled out of scheduling based upon structural features. In order to synthesize the OXY and M haptens under GMP, our team had to acquire Schedule II manufacturing licenses at our CDMO/CMO partners. While achievable, this process required a significant investment of time and funds, and logistic challenges for shipping vaccine components across sites and state lines, collaborations with CMOs or CDMOs. Schedule II manufacturing under GMP, preclinical Good Laboratory Practice (GLP) toxicity studies, and clinical implementation of these novel therapies. Academic, private, or government laboratories engaged in drug discovery and medication development typically hold Schedule I and II-V Researcher Licenses, which support early activities and pre-clinical testing of small molecules or modifications thereof (e.g., vaccines). However, scale-up and manufacturing most often involve shipping of small molecules across sites and state lines, collaborations with CMOs or CDMOs capable of synthesizing the lead compound are GMP, and such activities may require either a Schedule I or II Manufacturer or Distributor License. In order to pursue a Schedule I or II Manufacturer License, significant upgrades to the facility or laboratory footprint are required. While this may be feasible for Schedule II Manufacturer Licenses, it is quite time-consuming and expensive to do so for Schedule I Manufacturers. Such limitations may affect the development of small molecule analogs as well as vaccines or antibodies targeting fentanyl and its analogs. A critical aspect of the Schedule I definition is that the derivatives themselves have no known therapeutic indication. Ironically, the therapeutic potential of many Schedule I drugs will never be known precisely because they are scheduled.

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**Declaration of competing interest**

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AC is Professor and Associate Dean for Academic Affairs at the University of Maryland School of Pharmacy. In the past three years Dr. Coop has reviewed grants for the US Federal government without compensation, but has received compensation from both the federal government and Maryland state government for work as an expert witness in criminal trials related to analogs of controlled substances.

MHB is a Staff Scientist, and Chief of the Designer Drug Research Unit, Intramural Research Program of the National Institute on Drug Abuse, National Institutes of Health. He has no conflicts to disclose.

CWC is an Associate Professor of Pharmaceutical Sciences at Concordia University Wisconsin School of Pharmacy. In the past 5 years, he has received small honoraria for his services on behalf of the National Science Foundation (e.g., grant review) and academic centers (e.g., invited speaker).

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References


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