have overlapping expression patterns in neuronal tissues, including the hippocampus and several cortical regions (Dessauer *et al*, 2017). Studies with mice lacking either AC1 ($AC1^{-/-}$), AC8 ($AC8^{-/-}$), or both isoforms (double knockout mice, DKO) revealed that AC1 and AC8 are not required for acute pain responses; however, the behavioral responses to inflammatory stimuli (that is, formalin and CFA) were nearly eliminated or abolished in $AC1^{-/-}$ or DKO mice, respectively (Zhuo, 2012). Unfortunately, the DKO mice showed significant memory deficits, making it imperative to find agents that selectively target AC1. Dr Zhuo and colleagues identified the first selective small molecule inhibitor of AC1, NB001, and demonstrated efficacy in multiple chronic pain models in both mice and rats (Wang *et al*, 2011). NB001 has modest (14-fold) selectivity for AC1 *vs* the closely-related AC8 isoform and had activity consistent with AC1 inhibition in neuronal cells and tissues (Wang *et al*, 2011). We recently screened a small (3040 compounds) natural product-like chemical library and identified an additional small molecule that selectively inhibited AC1, ST034307 (Brust *et al*, 2017). ST034307 is a small chromone derivative with unprecedented selectivity for inhibiting AC1 *vs* the other AC isoforms. The precise site of AC1 engagement is unknown; however, ST034307 appears to have a mechanism of action that is unique from other known AC inhibitors. It was shown to dose-dependently reduce opioid dependence in a cellular model and inhibited allodynia in a phenotypic mouse model of inflammatory pain (Brust *et al*, 2017). These data support the development of additional selective AC1 inhibitors for the treatment of chronic pain conditions as potential alternatives to opioids.

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Novel Synthetic Opioids and Overdose Deaths: Tip of the Iceberg?

The United States is experiencing an unprecedented epidemic of opioid overdose deaths. Illicit heroin is an obvious culprit in the crisis and compelling evidence shows synthetic opioids, especially fentanyl, are having a major impact (Frank and Pollack, 2017). Fentanyl is a prescribed medication that is 50–100 times more potent than morphine. Fentanyl in the recreational (ie, non-medical) drug market is not diverted pharmaceuticals but is illicitly manufactured in Asian laboratories and trafficked via the Internet. Unscrupulous drug dealers are mixing fentanyl with heroin and most users are unaware of their fentanyl exposure.

An alarming new development in the opioid crisis is the increasing availability and misuse of novel synthetic opioids (NSOs) (Prekupec *et al*, 2017). NSOs include analogs of fentanyl and structurally distinct non-fentanyl compounds, which act as μ-opioid receptor agonists. NSOs are used as standalone products, heroin adulterants, or constituents of counterfeit pain pills. The role of NSOs in opioid overdose deaths is difficult to determine, because the substances are not detected by standard toxicology screens, which rely on immunoassays sensitive to heroin, its metabolites, and chemically related compounds. Fentanyl can be detected with a separate immunoassay, but fentanyl analogs may cross-react with the antibody; thus, identifying analogs requires sophisticated analytical methods such as mass spectrometry. In a study examining the presence of fentanyl analogs in opioid overdose deaths, 17% of cases that tested positive by fentanyl immunoassay were found to contain fentanyl analogs (eg, acetylfentanyl) when subjected to confirmatory testing with mass spectrometry (Petersen *et al*, 2016). Medical examiners and forensic toxicologists do not routinely check for the presence of NSOs; thus, the contribution of the substances to overdose deaths could be grossly underestimated.

N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furamide (furanylfentanyl) and 3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700) are prime examples of NSOs linked to analytically confirmed overdose deaths (Mohr *et al*, 2016) (see Figure 1 for structures). Furanylfentanyl is a fentanyl analog with a furan ring on the carboxamide moiety, whereas U-47700 is a non-fentanyl compound developed in the 1970s as a potential analgesic. Little information is available about the pharmacology and toxicology of furanylfentanyl, U-47700, or other NSOs, most of which were discovered decades ago. There is an immediate need for *in vitro* studies examining the potency and efficacy of NSOs in cells expressing μ-, δ-, and κ-opioid receptors. In addition, *in vivo* studies are warranted to investigate analgesic and reinforcing effects of the drugs in animal models, including opioid receptor knock out mice. The degree

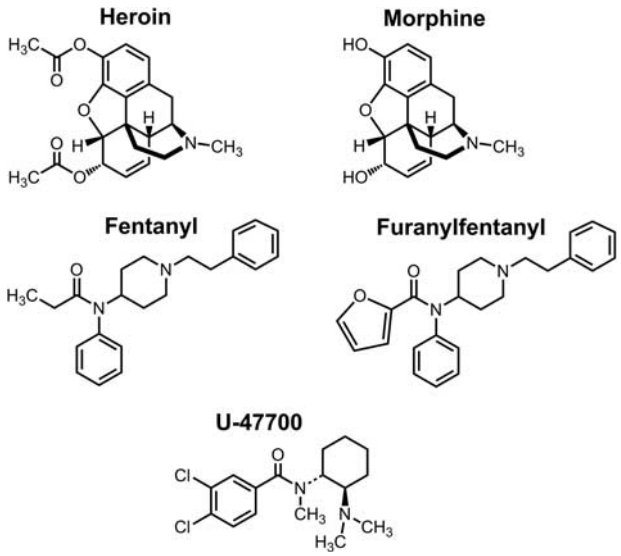

Figure 1. Chemical structures of heroin, morphine, fentanyl, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furamide (furanylfentanyl) and 3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700).

to which NSOs produce life-threatening adverse effects such as respiratory depression is largely unexplored.

Naloxone (ie, Narcan) is a competitive μ-opioid receptor antagonist that reverses the effects of heroin, fentanyl, and other opioids. Anecdotal evidence suggests that current naloxone dosing protocols (0.4–2 mg) are insufficient to rescue fentanyl overdose and previous research shows naloxone doses up to 20 mg were required to reverse the effects of fentanyl during an epidemic of overdose cases in Chicago during 2005–2006 (Schumann *et al*, 2008). Such observations may simply reflect the need for larger doses of naloxone to reverse high fentanyl doses, but could point to interaction of fentanyl with alternative non-opioid receptor targets after high doses. Whether greater-than-expected doses of naloxone are required to antagonize effects of highly potent NSO remains an open question. The recent emergence of the fentanyl analog, carfentanil, in the recreational drug market is especially troubling because this compound is 100 times more potent than fentanyl (Shoff *et al*, 2017). The potential risk from non-opioid compounds in the marketplace is well illustrated by 4-chloro-*N*-[(2Z)-1-[2-(4-nitrophenyl)ethyl]piperidin-2-ylidene]benzene-1-sulfonamide (W-18). Although initially touted as a highly potent opioid, recent evidence reveals that W-18 does not interact with μ-, δ-, or κ-opioid receptors; thus, effects of the drug will not be antagonized by naloxone (Huang *et al*, 2016).

To conclude, NSOs are contributing to the current epidemic of opioid overdose deaths. Basic research investigations aimed at characterizing the pharmacology and toxicology of NSO are needed as part of a comprehensive science-based response to the opioid crisis. In particular, preclinical studies are warranted to determine the sensitivity of analgesic, respiratory depressant, and lethal effects of fentanyl, carfentanil, and NSO to naloxone or other broader spectrum opioid antagonists such as levallorphan. Data from such studies will help to inform the public, influence drug scheduling decisions, and aid in strategies to remediate effects of the drugs in emergency and clinical settings.

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Opioidergic regulation of pain and pleasure in human social relationships

Affiliative bonds are the hallmark of human sociability, having evolved to support survival, reproduction, and nurturing of the offspring. Social relationships are associated with security and comfort. Such feelings could serve as safety signals, promoting incentive motivation towards social