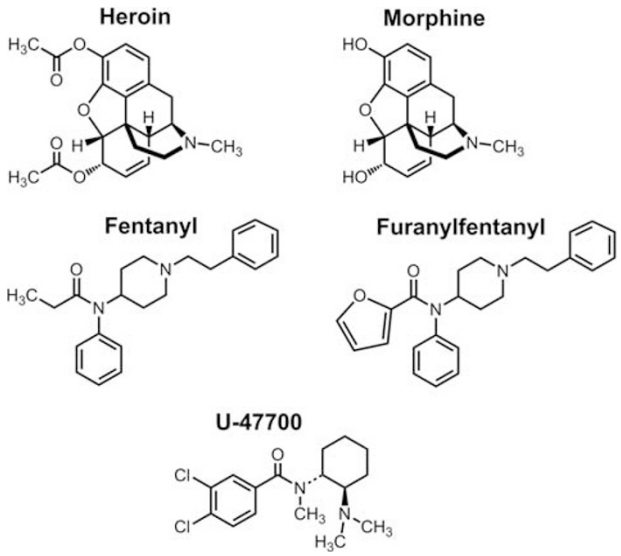

Figure 1. Chemical structures of heroin, morphine, fentanyl, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furamide (furanylfentanyl) and 3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700).

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

bonding. Building up on the seminal work by Jaak Panksepp and colleagues, recent genetic studies suggest that different neurochemicals including dopamine, oxytocin, and particularly opioid peptides regulate different aspects of sociability (Pearce *et al*, 2017). Human positron emission tomography (PET) studies have highlighted that the endogenous opioid system, best known for its role in pain and reward, supports also social bonding in humans. Prosocial behavior, such as social laughter, triggers endogenous opioid release in thalamus and insular cortex concurrently with increased calmness and amusement (Manninen *et al*, 2017). Such group-level opioid release via contagious laughter, rather than time-consuming dyadic bonding, may have allowed humans to significantly extend their social sphere. Yet conversely, also social rejections or losses may trigger similar endogenous opioid activation as social bonding (Hsu *et al*, 2013), paralleling the contribution of the opioid system to processing of purely sensory pleasure and pain in humans. Thus, the opioid system seems to modulate both motivation towards social contacts and support, and away from solitude.

Capacity for vicarious experience is a key feature of human sociability: feeling others' pain in our own mind may create a strong urge to help others in distress. Fusion imaging work combining PET with functional magnetic resonance imaging shows that the more opioid receptors humans have in their brain, the more strongly their frontocortical areas respond to seeing others' distress (Karjalainen *et al*, 2017). Similarly, placebo analgesia (modulated by the opioid system) also reduces empathy-related brain responses towards others' distress (Rutgen *et al*, 2015). Accordingly, the physical and vicarious pain might share the same neuromolecular basis, and opioidergic neurotransmission may facilitate more complex prosocial motivation than just social bonding.

Molecular imaging studies have also established that individual differences in endogenous opioid system function explains individual differences in sociability. In particular, opioid receptor availability in the frontal cortex—a region involved in variety of socio-emotional processes—predicts both the security of romantic attachment bonds (Nummenmaa *et al*, 2015) as well as the tendency for prosocial expressions such as laughter in social settings (Manninen *et al*, 2017). Genetic as well as experience-dependent plasticity of the endogenous opioid system might thus constitute an important precursor for trait-like differences in social behavior, including prosociality and helping behavior.

All in all, these results extend pharmacological work in non-human primates showing that opioid agonists decrease and antagonists increase social grooming (analogous prosocial behavior to human social laughter), suggesting a shared opioidergic bonding mechanism across humans and other primates. Furthermore, the recent data show that in humans the opioid system has evolved to serve not only reproductive or maternal dyadic bonding, but also large-scale affiliative bonding and altruistic behaviour such as helping triggered by seeing others—even unfamiliar individuals—in distress.

Most humans strive for social contacts throughout their lifespan, and lack of social contacts has significant negative consequences for both psychological and somatic health. Accordingly, properly functioning endogenous opioid system could be an important precursor for psychological resiliency and well-being in general. This may explain why disruption of the endogenous opioid system by, for example, heroin abuse may lead to antisocial behavior. However, the specific role of the opioid system in different types of social relationships (such as romantic versus affiliative) needs to be resolved in future studies.

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Modulating Amygdala–Hippocampal Network Communication: A Potential Therapy for Neuropsychiatric Disorders

Contextual processing imbues appropriate salience to our experiences and facilitates flexible behavioral adaptation. Dysfunction in contextualizing information increases the risk of inappropriate responses to environmental conditions and has been implicated in a broad range of psychopathologies, including post-traumatic stress disorder, schizophrenia, and substance abuse disorders (Maren *et al*, 2013).

Given the essential role of contextual processing in adaptive behavior and its derangement in neuropsychiatric disorders, recent research has focused on