The United States is in the midst of a horrific problem. The rampant misuse of opioid drugs (both prescribed and illegal), now known as the Opioid Crisis, has had grave effects on both the public health and the well-being of our society. In 1 year, 2017, it is estimated that almost as many Americans died from opioid-related overdose as died in the entire Vietnam War [1]. In response to the problem, the White House has declared the Opioid Crisis a national Public Health Emergency under federal law [2].

The causes of the Opioid Crisis are complex and multifaceted and a solution will require a Herculean, integrated effort from disparate components of society. Changes in both the public and private sectors (e.g., revisions in: health care policy; medical education; business regulation; deployment of existing medications; local and state justice systems) will be needed to address this crisis. In an effort to leverage science to help address the problem, the National Institutes of Health (NIH) has launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to the Opioid Crisis [3]. This initiative will nearly double funding for research on opioid misuse/addiction and pain. As part of the NIH, the National Institute on Drug Abuse (NIDA) is devoted to addressing this crisis in multiple ways. NIDA will coordinate four overarching research projects around the country: the Focused Opioid Use Disorder (OUD) Medications Development Research Project; the HEALing Communities Study; the Clinical Trials Network OUD Research Enhancement Project; and the Justice Community Opioid Innovation Network [4]. The medication development component of this four-pronged effort includes aiding the development of novel pharmacotherapies, behavioral therapies and devices for the treatment of opioid overdose and OUD.

Our science can have political, economic and social ramifications. Indeed, the introduction of safe and effective therapeutics, while unlikely to be a panacea, has the potential to transform not only health outcomes for individual patients, but anachronistic societal attitudes towards diseases, especially brain diseases. In this regard, we hope that the introduction of new safe and effective medications for OUD will enlighten the public discourse around opioid addiction and those suffering from it. In an effort to specifically speed the development of pharmacotherapies for the treatment of OUD and reach NIDA’s stated goal of 15 Investigational New Drugs (INDs) and 5 New Drug Applications (NDAs) submitted to the Food and Drug Administration (FDA), NIDA’s Division of Therapeutics and Medical Consequences (DTMC) has created a list of medication development priorities.

The mechanisms listed in Table 1 are NIDA’s DTMC highest priority pharmacological targets for the development of novel therapeutics to treat opioid overdose and OUD in the near term. The list does not include mechanisms of existing OUD medications and the mechanisms are listed in no particular order. While the existing medications (e.g., buprenorphine, methadone, naltrexone, lofexidine) have demonstrable utility in the treatment of OUD, they are not without limitations. Indeed, problematic residual symptoms and discontinuation rates plague these treatments [5, 6], leaving a deceptively cavernous un-met medical need that could be addressed, at least in part, by new medications.

Our goal is to help deliver new treatment options to the millions of patients and physicians battling OUD. At this point in time, we feel compounds with the mechanisms-of-action listed in Table 1 have the highest probability of a path to FDA approval for the treatment of some aspect of OUD in the near term. An important component of this list are allosteric modulators. Based on their suppression/ augmentation of endogenous responses, negative allosteric modulators (NAMs) and positive allosteric modulators (PAMs) may provide more physiologically relevant effects compared with agonists and antagonists acting on the same receptor, which may ultimately result in improved clinical outcomes [7]. It is important to note that due to the complexity of the addiction cycle, different stages of the disease (e.g., transition from sporadic to chronic use, acute withdrawal, delayed relapse) are likely to have different (albeit overlapping) pathophysiology [8]. Thus, there is unlikely to be a “silver bullet” among these mechanisms for the treatment of OUD and medications with these mechanisms-of-action are likely to be useful at different stages of the addiction cycle. In addition, it is important to remember, as has been clearly demonstrated from the treatment of major depressive disorder [9], pharmacotherapies can have greater impact when paired with effective psychosocial interventions. Indeed, two key components of NIDA’s treatment development efforts are the development of novel behavioural and device treatments. Ultimately, we anticipate multiple medications, integrated with both psychosocial interventions and potentially devices, employed in an orchestrated fashion, will be needed to achieve truly effective treatments “tailored” for maximal efficacy in different individuals.

We have determined our “most wanted” mechanisms based on data from published literature and internal studies that we feel have the most direct relevance to desirable treatment effects and clinical endpoints for OUD. Importantly, most of these mechanisms are active in more than one model, and for more than one drug of abuse, which presents the intriguing
trials or laboratory studies that will de- 
the predictive validity of the preclinical data; and (3) clinical 
fi 
tri 
trials that will de- 
neuroimmune targets [16]. We anticipate, and fervently hope, 
assays for clinical ef- 
possibility of their potential ef- 
PAM negative allosteric modulator, NAM negative allosteric modulator, AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GABA γ-aminobutyric acid, NOP nociceptin opioid peptide receptor, ORL opioid receptor like, mGlur metabotropic glutamate receptor, SHT 5-hydroxytryptamine, MOP mu opioid protein
Other mechanisms of interest:

SHT2C agonists or PAMs, with or without SHT2A antagonist/NAM activity [41, 42]
Biased Mu opioid agonists or NAMs [43, 44]
NOP/MOP bifunctional agonists or PAMs [45, 46]
Respiratory stimulants (including nicotinic agonists) [47, 48]

We do not propose this list as a static be-all and end-all; but, rather, a dynamic clarion call that will evolve with advances in the field. Indeed, we hope that proposing this list will help spur the future research that will ultimately antiquate it. The list is biased towards proximal action as, quite literally, people are dying, in this regard, mechanisms that have compounds already in, or close to, clinical development and have a high probability of a path to FDA approval have been emphasized. As these mechanisms are tested in the clinic, they will move off the list either as new therapeutics for the millions of patients battling OUD or as “learning opportunities (as there is much to be learned even from clinical trial “failures”), Of course, there is robust, on-going research into uncovering additional mechanisms, not yet on the list, that could be useful for the treatment of OUD. Examples of entirely new directions for novel OUD treatments include epigenetic [14], micro RNA [15] and neuroimmune targets [16]. We anticipate, and fervently hope, additional research will help new mechanisms “percolate up” to warrant inclusion on this list. Additionally, we hope to engender vigorous scientific debate on what should, and should not, be on this list. We welcome your feedback, encourage suggestions for additional novel mechanisms of action, and, as always, invite more data!

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