Recent Advances in Pharmacologic Treatments for Opioid Use Disorder

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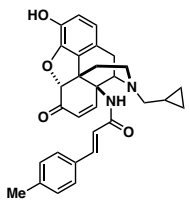
Current Status of the Opioid Epidemic and OUD Medications

The United States is currently in the midst of an opioid epidemic, which has resulted in over 500,000 opioid-related overdose deaths since 1999.[1] Individuals that suffer from opioid use disorder (OUD) participate in the chronic use of opioids, typically mu opioid receptor (MOR) agonists, despite significant reduction in quality of life. Although they are at an increased risk of opioid overdose death, as of 2022, only 25.1% of US adults with OUD received OUD medications for treatment.[2] There are currently three main medications that are FDA approved for the treatment of OUD: methadone (MOR agonist), buprenorphine (partial MOR agonist), and naltrexone (MOR antagonist).[3] Although these medications have been used for decades, there are several limitations of these treatments that can hinder patient treatment, particularly drug-drug interactions, treatment access, opioid tolerance, and short durations of action.[4] With the rise in synthetic opioid overdose deaths over the past several years, the US needs creative pharmacologic strategies for the treatment of OUD. This seminar will discuss recent advances in the development of new OUD medications and strategies, with a particular emphasis on their efficacy compared to current OUD medications.

MCAM as a MOR Antagonists for OUD

Current strategies for improving OUD medications, particularly MOR antagonists, focus on the development of improved, slow release formulations of naltrexone; however, there is work being done to investigate a promising small molecule MOR antagonist as an alternative to naltrexone, methocinnamox (MCAM) (Fig. 1).[4,5] MCAM has recently been shown to have high efficacy towards reducing fentanyl seeking behaviors and appears to have an enhanced duration of action of two weeks.[5] It is widely believed that MCAM's pseudo-irreversible binding to the MOR allows for such a prolonged duration of action.[5] MCAM is a promising candidate for OUD treatment due to its enhanced efficacy for synthetic opioids, its prolonged duration of action, and its minimal drug-drug interactions compared to naltrexone in rhesus monkey models.[5]



MCAM
MOR Antagonist

Figure 1: MCAM Structure

An Anti-Heroin Vaccine for OUD Treatment

While MCAM appears to be a promising candidate for OUD treatment as a MOR antagonist, there is a need for innovative strategies for OUD treatment, such as the use of drug-conjugate vaccines. Vaccines have been a vital tool for preventing infectious diseases for centuries and researchers have taken inspiration from these vaccine treatments through drug conjugate vaccine campaigns for the treatment of psychoactive drugs in the 1970s and 1990s.[3] While these early drug conjugate vaccines were abandoned, recent work is being done to develop an anti-heroin vaccine with improved efficacy through the optimization of hapten design, carrier protein, and adjuvant formulation.[6] A promising early candidate to come from this heroin conjugate vaccine campaign is HerCOOH conjugated to tetanus toxoid (TT) and formulated with alum and CpG oligodeoxynucleotide (Fig. 2). This vaccine formulation is efficacious in mouse and rhesus monkey models for the treatment of OUD for over eight and six months, respectively.[6]

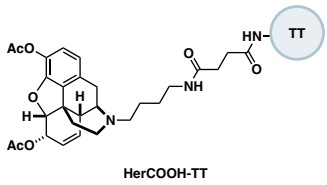


Figure 2: Anti-Heroin Vaccine Structure

An Anti-Fentanyl Vaccine for OUD Treatment

With the rise of fentanyl-induced opioid deaths over the past ten years, researchers sought to take inspiration from the previously described HerCOOH-TT campaign for an anti-heroin vaccine to synthesize an anti-fentanyl vaccine.[6,7] Adjuvants to improve fentanyl-antibody production were also investigated and it was found that a fentanyl-like hapten (F_1) conjugated to a cross reactive diphtheria toxoid carrier protein (CRM_1) and formulated with the TLR8 agonist INI-4001 has enhanced abilities to reduce fentanyl efficacy and increasing anti-fentanyl antibodies in rat and porcine models (Fig. 3).[7] This anti-fentanyl vaccine shows immense promise towards combatting OUD through its enhanced ability to prevent fentanyl from penetrating the CNS and its reduced drug-drug interactions with respect to traditional OUD medications.[7]

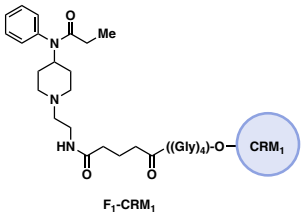


Figure 3: Anti-Fentanyl Vaccine Structure

Towards the Future of OUD Treatment

Although the current medications for OUD treatment have been used for decades, the rise in synthetic opioids with enhanced potencies highlights the need for new and creative treatments to mitigate synthetic opioid use and overdose. These new anti-opioid vaccines and MCAM hold much promise as new and effective treatments to combat the opioid epidemic.

References.

(1) NIDA. *Drug Overdose Deaths: Facts and Figures.* **2024**.; (2) *MMR CDC*. **2024,** *73*(25), 567-574.; (3) *J. Am. Chem. Soc.* **2019**. 141, 1798-1806.; (4) *Pharmacy.* **2022**. *10*, 48.; (5) *Neuropsychopharmacol*, **2020**, *45*, 1986-1993.; (6) *J. Am. Chem. Soc.* **2017**, *139* (25), 8601-8611.; (7) *Npj Vaccines,* **2023**, 8, 107.