**Supplemental Table 2.** Examples of promising research leads in the treatment of addiciton

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| **Project** | | **Rationale** | **Status** |
| **Vaccines** | Heroin and fentanyl  Cocaine | Active immunotherapies could prevent drug entry into the brain protecting against relapse and the drug’s adverse effects (2). A heroin vaccine that elicited IgG antibodies against heroin and its psychoactive metabolites was shown to markedly attenuate heroin’s potency (3). In a more recent proof of principle development, an admixture vaccine against fentanyl-laced heroin inhibited drug entry into the brain after administration of an intravenous bolus of heroin contaminated (10% w/w) with fentanyl (5). | Researchers are working at Scripts Research Institute) on a vaccine against heroin at Minneapolis Medical Research Foundation on an oxycontin vaccine at Minneapolis Medical Research Foundation on a fentanyl vaccine and. And, in collaboration with NIDA, the U.S. Military HIV Research Program (MHRP) has recently reported on a new experimental heroin vaccine that was capable of inducing antibodies that prevented the drug from crossing the blood-brain barrier in mice and rats (9). Importantly, vaccinated mice had reduced heroin-induced hyperlocomotion following a heroin challenge. |
| At Corneil researchers are developing an anti-cocaine vaccine (dAd5GNE) by crosslinking adenovirus capsid with a cocaine analog to produce anti-cocaine antibodies to prevent cocaine from reaching the brain. | Corneil researchers in partnership with Opiant are conducting a first-in-man clinical trial in individuals with cocaine use disorder that will evaluate antibody titers and safety. The first cohort of 10 subjects (was completed with no significant safety issue. |
| **Monoclonal antibodies** | Methamphetamine (METH) | Passive immunization delivers polyclonal or monoclonal antibodies and is particularly suited for acute treatment of an overdose. A passive/active combination antibody therapy approach in rats achieved early high anti-METH antibody response, which a longer-term response that persisted for up to 4 months (4) . | InterveXion Therapeutics has completed 2 preclinical studies of a METH conjugate leading to an IND. A phase 2a clinical trial was just started in an outpatient setting. |
| **Meds** | Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (7) | Naltrexone blocks opioid receptors -which are implicated in drug reward-, and is prescribed for the treatment of alcohol and opioid use disorders. Bupropion is a norepinephrine-dopamine reuptake inhibitor prescribed for smoking cessation. Contrave (naltrexone + bupropion) has FDA approval as adjunct to a reduced-calorie diet and physical activity for weight management in obesity. A pilot study showed positive effects of naltrexone + bupropion combination for methamphetamine use disorder (6). | Phase III clinical trial designed to determine if a combination of extended-release naltrexone and bupropion will help stop or reduce methamphetamine use.  Recruitment will continue until end of 2018. |
| Orexin antagonists for the treatment of Opioid use disorders | Orexin receptors play a key role in the induction of reward-related behaviors to drugs of abuse, and in the NAc, they are involved in morphine-induced CPP. Blocking these receptors attenuates the acquisition of morphine CPP, although orexin-1 receptors appear to play a more dominant role in development of morphine reward-related behaviors (1). | NIDA is planning to conduct a trial of suvorexant for OUD. Suvorexant (OX1 and OX 2 nonselective antagonist) is clinically available for the treatment of sleep disorders. NIDA is supporting the development of OX-1 antagonists for opioids, nicotine and cocaine. |
| **Devices** | rTMS as a potential treatment for cocaine use disorder | TMS was shown to be effective to treat depression and preliminary data shows potential benefit to treat various SUD. Since patients with CUD often display PFC hypoactivity, excitatory (rTMS) targeting PFC areas has been proposed for its treatment. | Researchers in Italy are conducting a, randomized, double-blind, placebo-controlled, pilot trial, to assess the efficacy of rTMS on cocaine intake (8). |
| Non-invasive intermittent theta burst stimulation (iTBS) of dPFC for OUD | iTBS will be used to modulate activity and connectivity in 2 networks: ECN (dorsolateral prefrontal cortex hub) and SN (insula hub). The purpose is to modulate brain regions that are key to craving, pain and cognition. It will evaluate whether iTBS can improve cognitive set shifting, impulsivity, hyperalgesia in OUD. | Will investigate the effects of iTBS to the left dorsolateral prefrontal cortex (DLPFC) on craving and opioid consumption in OUD patients undergoing buprenorphine therapy. |

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