Clinically utilized nalfurafine combined with naltrexone prevents excessive alcohol drinking and “relapse”

Alcohol addiction poses massive public health costs [~15 million adult alcoholics with economic cost > $200 billion/year in the US]. Pharmacological studies in rodents have demonstrated that kappa-opioid receptor (KOR) agonists decrease alcohol drinking and reward. However, “classic” KOR agonists produce sedation and dysphoria in humans, and those side effects limit their clinical use potential.

Nalfurafine was the first and only currently clinically approved KOR agonist as anti-pruritus treatment with lack of side effects in humans (sedation, depression, or dysphoria), especially in a recent post-market report on safety and efficacy of Remitch® (nalfurafine hydrochloride at 2.5-5 ug/day) in more than 4000 patients. Nalfurafine is an orally available small molecule and central-acting KOR agonist; with a long duration of action (biological half-life 14-25 hours).

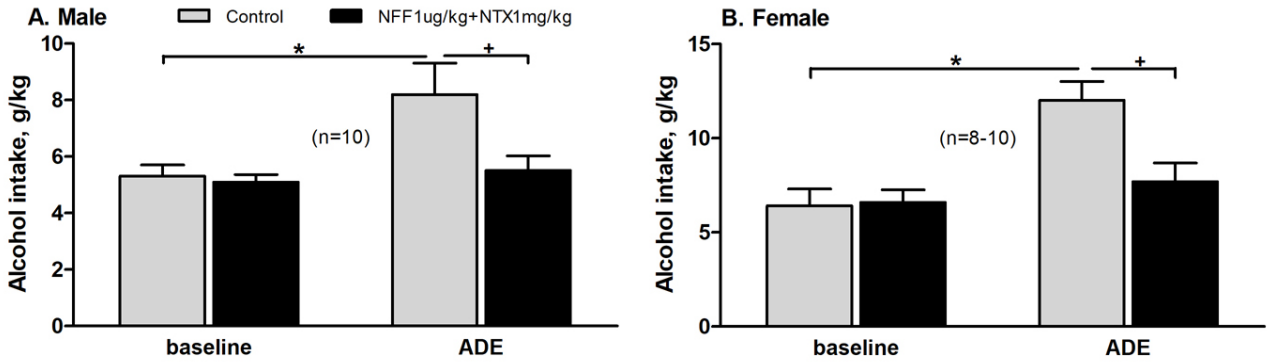

Fig. 1. Effects of nalfurafine (NFF, 1ug/kg) combined with naltrexone (NTX, 1 mg/kg) on alcohol “relapse” intake in an alcohol deprivation effect (ADE) model in males (A, n=10) and females (B, n=8-10) after 1 week of abstinence from 3-week excessive alcohol drinking.

Recently, we examined pharmacological effects of nalfurafine on alcohol drinking and found: (a) nalfurafine dose-dependently reduced alcohol consumption in an excessive drinking paradigm (an appropriate animal model for alcohol dependency); and (b) of importance, repeated administration of nalfurafine decreased alcohol consumption without showing any tolerance. To determine potential undesirable effects, we further observed that nalfurafine *did not* produce anhedonia (sucrose and saccharin drinking), anxiety-like (elevated plus maze test), or sedation (spontaneous locomotor activity) behaviors. Together, these exciting data suggest a potential novel approach to treat alcoholism, by re-purposing clinically utilized nalfurafine.

As the multiple actions of alcohol in the brain, combination medications targeting multiple neuronal

systems have enhanced efficacy over mono-therapy strategies. Though naltrexone is partially effective, the single-target pharmacotherapy has limited therapeutic value, suggesting a need for better efficacy. Our study demonstrated that the effects of the combination of nalfurafine with naltrexone were greater than those of either drug alone. This interesting approach is also to select the two compounds at low doses, with few side effects, which have the potential to decrease alcohol when given together as a novel formulation. Combining low-dose naltrexone with nalfurafine is an effective strategy for decreasing excessive alcohol. From the clinical development standpoint, this strategy benefits from the fact that each of these drugs are already used in humans, so combining them at lower doses for human use is a low-risk approach.

As alcohol relapse is an important target for medications development for alcoholism, we further investigated the pharmacological effects of nalfurafine using mouse “relapse” model to ascertain its potential as an anti-relapse compound. Specifically, nalfurafine alone prevented alcohol “relapse” (the key features of alcoholism) in a dose-dependent manner and nalfurafine plus naltrexone [both at low doses] is more effective (Fig. 1).

Together, our goal is to advance the translation of basic research discoveries into breakthrough medications for the clinic: develop a combination-based novel formulation (nalfurafine+naltrexone) to prevent excessive drinking, “craving” and relapse of alcoholism. Both the small molecules have been used in the clinic with documented safety, and thus there is fast translational potential for the novel anti-alcoholism formulation. This new finding is of potential importance to the field of pharmacotherapeutics for alcohol use disorders.

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