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# The efficacy of a low dose combination of topiramate and naltrexone on ethanol reinforcement and consumption in rat models☆,☆☆

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ABSTRACT

*Rationale:* Combined medication approaches, by targeting multiple neurotransmitter systems involved in alcohol use disorders (AUDs), may be more efficacious than single-medication approaches.
*Objectives:* We examined, in animal models of consumption and reinforcement, the combined effects of naltrexone (an opioid antagonist) and topiramate (a GABA/glutamate modulator), two medications that have shown promise for treating AUDs, hypothesizing that their combination would be more efficacious than either alone.
*Methods:* The effects of naltrexone and topiramate on ethanol consumption were examined in alcohol preferring (P) rats (N = 10) and in rats from their background strain (Wistar, N = 9) using conditions that induce high levels of consumption (24-h, 3-bottle, free-choice procedure). Low doses of each medication (1 mg/kg, naltrexone; 10 mg/kg, topiramate) were selected in an attempt to maximize their combined efficacy while minimizing potential side-effects. Their effects on ethanol reinforcement were assessed under a progressive-ratio schedule in additional groups of (N = 22) P rats. A moderate dose of topiramate (20 mg/kg) was also included to verify topiramate's efficacy on its own.
*Results:* In P rats, but not in Wistar rats, the combination effectively and persistently reduced consumption; whereas, neither dose alone was effective. The combination and naltrexone alone were equally effective at reducing ethanol reinforcement; however, with the combination, but not naltrexone alone, this effect was selective for ethanol. All treatments produced a similar decrease in home-cage food consumption. The 20 mg/kg dose of topiramate also effectively reduced ethanol consumption and reinforcement.
*Conclusions:* With greater efficacy and fewer side-effects, the combination shows promise as a treatment for AUDs.



## 1. Introduction

Alcohol use disorders (AUDs), which include alcohol abuse and dependence, are responsible for vast health, social, and economic problems. AUDs affect 30% of the U.S. population within their lifetime, but only about a fourth of these individuals receive any kind of treatment (Hasin et al., 2007). Chronic exposure to alcohol results in enduring neuroadaptations in multiple signaling pathways, including opioid, dopamine, glutamate, and γ-aminobutyric acid (GABA) pathways (for reviews see Chastain, 2006; Clapp et al., 2008; Koob and Volkow, 2009; Heinz et al., 2009a), that give rise to lasting cognitive and behavioral changes (SAMHSA, 2009; for review see Hoffman et al., 2000). These neuroadaptations contribute to the multiple components of AUDs: tolerance, withdrawal, craving (both alcohol craving and withdrawal relief craving), drug reinforcing properties, etc. (for review see Gilpin and Koob, 2008; Heinz et al., 2009b; SAMHSA, 2009; for review see Hoffman et al., 2000). Currently approved medications are thought to target the neurotransmitter pathways underlying one or more of these components, such as acamprosate, which is believed to reduce withdrawal symptoms and craving through modulation of N-methyl-D-aspartic acid (NMDA) receptors (for review see Rösner et al., 2010). This and other single-pathway targeted pharmacotherapies for AUDs have shown modest therapeutic value over placebo, but greater efficacy is needed. Combination medications, by targeting multiple neurotransmitter pathways implicated in different components of AUDs, are likely to have enhanced efficacy over the traditional single-medication approach.

Naltrexone, an opioid receptor antagonist, is one of three currently approved treatments of AUDs in humans that is particularly effective at decreasing heavy drinking (Chick et al., 2000), likely by reducing

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the reinforcing effects of alcohol (Volpicelli et al., 1995; King et al., 1997; for review see Heilig and Egli, 2006). Treatment with naltrexone also reduces self-administration of ethanol in animal models (Stromberg et al., 1998; Gonzales and Weiss, 1998; Middaugh and Bandy, 2000). Naltrexone's effects are proposed to be mediated through blockade of μ-opioid receptors on medium spiny neurons in the nucleus accumbens that may prevent ethanol-induced dopamine release (for review see Unterwald, 2008). There is also evidence to suggest that these effects are mediated via a dopamine-independent mechanism (Self and Nestler, 1996). In alcohol-dependent humans, in addition to decreasing alcohol consumption, naltrexone has been shown to block cue-induced activation of the reward pathway (Myrick et al., 2008), reduce craving (O'Malley et al., 2002) and decrease the subjective effects of alcohol (Volpicelli et al., 1995; King et al., 1997). Despite these findings supporting the efficacy of naltrexone in reducing several of the individual components involved in AUDs, its beneficial effects have not consistently translated to enhanced abstinence or reduced consumption in alcohol-dependent individuals. Clinical studies of naltrexone have variable efficacy on reducing alcohol consumption, with meta-analyses showing a small effect size (for review see Garbutt, 2010).

Topiramate (a GABA/glutamate modulator) is a currently approved treatment for epilepsy that has also shown promise as a potential treatment for AUDs. Topiramate facilitates $GABA_A$-mediated inhibitory transmission while contemporaneously antagonizing AMPA and kainate glutamate receptors, among other actions (Johnson, 2004). Studies in humans have shown that treatment with topiramate reduced several measures of alcohol use, such as number of drinks/day and drinks/drinking day as well increased abstinence (Johnson et al., 2003, 2007). Topiramate's effects on craving are less clear, with one study reporting lower levels of craving (Johnson et al., 2003), but another showing that while topiramate reduced drinking, it did not decrease reactivity to ethanol-cues or self-reported craving (Miranda et al., 2008). Topiramate has also been reported to reduce ethanol consumption in rats (Knapp et al., 2007; Breslin et al., 2010; Lynch et al., 2011) and in C57BL/J mice (Gabriel and Cunningham, 2005). While the mechanism of topiramate's effects on alcohol use has yet to be identified, it was originally postulated that by both inhibiting glutamate and facilitating GABA function, topiramate might suppress corticomesolimbic dopamine, thus decreasing the reinforcing effects of alcohol (Johnson, 2004). In preclinical studies, topiramate reduces progressive-ratio (PR) responding for ethanol in rats (Hargreaves and McGregor, 2007), supporting the theory that topiramate reduces the reinforcing effects of ethanol; however, these effects appear to be mediated via glutamatergic, rather than dopaminergic signaling (Lynch et al., 2013).

The goal for this study was to determine the effects of naltrexone and topiramate, alone and in combination, in rats that had prolonged access to ethanol under conditions that induce high levels of drinking. Low doses of each medication, which either do not affect or only modestly affect alcohol-related behaviors on their own, were selected in an attempt to maximize their combined efficacy while minimizing potential side-effects. A similar low-dose naltrexone–topiramate combination approach was recently found to effectively reduce alcohol consumption and reinforcement in mice consuming ethanol under sub-chronic and limited access conditions (Navarrete et al., 2013). In this study, effects of treatments on ethanol consumption were assessed in groups of rats given access to ethanol under a 24-h, three-bottle, free-choice paradigm. These effects were examined in both alcohol-preferring (P) rats and rats of its background strain (Wistar) given our recent work indicating selective effects of topiramate treatment based on a genetic and/or behavioral phenotype (Lynch et al., 2011, 2013). The effects of treatments were also assessed on ethanol reinforcement in another group of P rats tested under a PR schedule after prolonged exposure under the same free-choice conditions. We hypothesized that this combination treatment, by modulating multiple signaling pathways that are known to be involved in AUDs (i.e. opioids, glutamate, GABA, dopamine), would be more efficacious than either alone at decreasing ethanol consumption and reinforcement.

## 2. Methods

### 2.1. Animals and housing

Male P rats (N = 32) from the 73–74th generations were obtained from the Indiana Alcohol Research Center's Animal Production Core (Indianapolis, IN). Male Wistar rats (N = 9), the background strain of P rats, were obtained from Charles River Laboratory (Wilmington, MA). The P line of rats has been selectively bred and characterized by numerous studies as a valid animal model of excessive ethanol drinking behavior (Bell et al., 2006). Rats were single-housed in clear, polycarbonate cages in a room maintained on a 12:12 light/dark cycle (lights on at 7:00 AM). All animals were allowed a 1 week habituation period before the start of ethanol consumption. Animals were 11–12 weeks old at the start of the experiments. Food and water were provided ad libitum, and animals were weighed twice weekly. At the start of the treatment phase, body weights were between 450 and 550 g. By the end of the treatment phase, animals had increased their body weights by approximately 5%. Animal health was monitored daily by trained laboratory staff and all animal protocols were approved by the Animal Care and Use Committee at the University of Virginia.

### 2.2. Drugs

Ethanol solutions (8% v/v, 10% v/v, 16% v/v) were prepared from 190 proof absolute ethyl alcohol (Pharmco-AAPER, Brookfield, CT, USA) and diluted using tap water. Naltrexone HCl and Topiramate HCl were purchased from Sigma-Aldrich (St. Louis, MO). Both compounds were dissolved in 0.9% sodium chloride and sterile water and administered intraperitoneally at a volume of 1 ml/kg.

### 2.3. Experiment 1: procedure for ethanol consumption

P rats (N = 10) and Wistar rats (N = 9) were given 24-h access to two different concentrations of ethanol solution (8% v/v and 16% v/v) along with a bottle containing water under a free-choice procedure. Intake of ethanol and water solutions was determined daily with fresh solutions presented several times a week. Sipper tubes contained a ball bearing at the tip to prevent leakage. Food intake was measured daily at the same time as liquid consumption. To most accurately model the chronic exposure that is characteristic of human AUDs, we began treatments after a minimum of 6 months of ethanol experience. Prolonged access, defined in previous studies with ethanol experience ranging from 2 to 16 months, is associated with neurological changes that affect GABA, glutamate, and opioid receptor function (Eravci et al., 2000; Darstein et al., 1998; Hölter et al., 2000).

The effect of topiramate and naltrexone on ethanol consumption was examined on a stable baseline (defined as no increasing or decreasing trend in ethanol consumption, with a variation of less than 1 g/kg/day over three consecutive days) using a within-subjects, Latin-square design with compounds administered in random order. Baseline was re-established prior to each treatment and a minimum of 7 days separated each test session. On test days, a single treatment of topiramate (10 mg/kg), naltrexone (1 mg/kg), their combination (10 mg/kg topiramate/1 mg/kg naltrexone), or an equal volume of saline was administered intraperitoneally during the daily weigh sessions that were conducted between 12:00 PM and 1:00 PM, with water and ethanol consumption measured 24 h after each injection. This dose of naltrexone was selected based on previous research showing it to modestly and selectively reduce ethanol self-administration in Wistar rats (Stromberg et al., 1998; Kuzmin et al., 2008). Although higher doses have also been reported to reduce ethanol consumption (2.5–10 mg/kg), these doses also produce non-specific effects (i.e. decrease water consumption, produce motor effects; Bienkowski et al., 1999; Goodwin et al., 2001; Escher and Mittleman, 2006). The dose of topiramate was selected based on our previous findings showing