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Acute and chronic administration of a low-dose combination of topiramate and ondansetron reduces ethanol's reinforcing effects in male Alcohol Preferring (P) rats

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Abstract

Topiramate (a GABA/glutamate modulator) and ondansetron (a serotonin-3 antagonist) have shown promise as treatments for alcohol use disorders (AUDs), although efficacy is modest/variable for both medications. We recently showed in animal models of consumption and relapse that acute treatment with a combination of these medications was more efficacious than either alone. To determine whether the mechanism for its beneficial effects is through modulation of ethanol's reinforcing effects, we measured the effect of this combination in male alcohol preferring (P) rats (N=22) responding for ethanol under a progressive-ratio (PR) schedule. Low doses, which either do not affect (ondansetron; 0.001 mg/kg) or only modestly affect (topiramate; 10 mg/kg) alcohol-related behaviors on their own, were selected in an attempt to maximize their combined efficacy while minimizing potential side-effects. In addition to acute treatment (1 day), the effects of chronic administration (10 days) were examined in an attempt to model human treatment approaches. The effects of the combination were compared to the low dose of topiramate alone hypothesizing that the combination would be more efficacious than topiramate alone. While both topiramate and the combination similarly reduced PR responding for ethanol following acute treatment and during the initial phase of chronic treatment (days 1–5), after repeated administration (days 6–10), only the combination produced a sustained reduction in ethanol-maintained responding. These results suggest an advantage of the combination over topiramate alone at producing a sustained reduction in ethanol's reinforcing effects following prolonged treatment, and lend further support for its use as a potential treatment for AUDs.

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Keywords

Alcohol Preferring (P) Rats; Ethanol; Ondansetron; Topiramate; Combination Treatment

Alcohol use disorders (AUDs) affect 30% of the US population and incur vast social, economic, and health costs (Substance Abuse and Mental Health Services Administration, 2009). Despite its prevalence, reliably efficacious treatments are still not well established. Recently, combination pharmacotherapies that modulate multiple molecular targets of alcohol use have shown promise over the current single medication approach. One such treatment is a combination of topiramate, a gamma-amino-butyric acid (GABA)/glutamate modulator, and ondansetron, a serotonin (5-HT₃) antagonist. Given complex ethanol-mediated interactions between serotonergic systems and glutamatergic and GABAergic transmission (Koob et al., 1998; Heinz et al., 2009), the potential benefit of this combination treatment is that the effects of one medication can be augmented by modulation of an additional pathway with the second. Additionally, both of these medications are thought to indirectly modulate corticomesolimbic dopamine (Johnson, 2004a; Johnson, 2010), an important component of the reinforcing effects of ethanol (Gonzales, Job, & Doyon, 2004; Johnson, 2010).

Glutamate and GABA are key neurobiological targets of alcohol, with evidence showing that repeated ethanol exposure causes increased glutamatergic input and hyperexcitable GABA neurons in the ventral tegmental area (for review see Johnson, 2004b). Topiramate has been investigated as a potential therapy for AUDs due to its ability to modulate these neurotransmitter systems (Johnson, 2004a). In humans, treatment with topiramate reduces alcohol drinking and increases abstinence (Johnson et al., 2003; Johnson, Ait-Daoud, Akhtar, & Ma, 2004; Johnson et al., 2007; Miranda et al., 2008). In rodent models, acute administration with topiramate reduces both ethanol consumption (Breslin, Johnson, & Lynch, 2010; Lynch, Bond, Breslin, & Johnson, 2011) and PR responding for ethanol (Hargreaves & McGregor, 2007). However, there is evidence that with chronic administration, though initially effective, topiramate may lose its ability to decrease the reinforcing effects of ethanol (Hargreaves & McGregor 2007). Other studies report consistent reductions in ethanol consumption with chronic administration (Nguyen, Malcolm, & Middaugh, 2007; Zalewska-Kazubska et al., 2013), suggesting that topiramate may be working through a component other than the reinforcing effects of ethanol to reduce intake.

Serotonin systems have also been implicated in AUDs. Lower serotonin levels have been linked to alcoholism in humans (Loving, 1999) as well as high ethanol drinking in selectively bred rat lines (McBride, Bodart, Lumeng, & Li, 1995; Murphy et al., 2002). Ondansetron, which selectively antagonizes the serotonin 5-HT₃ receptors involved in reuptake (Kenna, 2010), has been shown to reduce alcohol consumption (Johnson et al., 2000; Kranzler, Pierucci-Lagha, Feinn, & Hernandez-Avila, 2003), preference (Swift, Davidson, Whelihan, & Kuznetsov, 1996), and its subjective effects (Johnson, Campling, Griffiths, & Cowen, 1993). Additionally, ondansetron has been shown to be more effective at reducing alcohol consumption and craving in early-onset alcoholics compared to late-

onset alcoholics (Johnson et al. 2002). Both acute and chronic treatment with various 5-HT₃ antagonists, including ondansetron, have been reported to reduce ethanol consumption in rats (Beardsley, Lopez, Gullikson, & Flynn, 1994; Knapp & Pohorecky, 1993; Tomkins et al., 2002); however, efficacy is variable, and like the human data, may be restricted to genetically vulnerable populations (i.e., heavy drinking P rats; Lynch et al., 2011).

Although the combination of ondansetron and topiramate has not yet been examined in humans, based on the efficacy of these treatments on their own and the complex interactions of their target systems (i.e. serotonin, glutamate, GABA), this combination has potential for a promising treatment, particularly for early-onset alcoholics (Johnson, 2008; Johnson, 2010). In support of this idea, we recently showed that acute treatment with this combination reduced ethanol consumption and relapse in rodent models, with a greater efficacy of the combination over either medication alone in high drinking P rats (Lynch et al., 2011). However, this combination's effects have not yet been examined under chronic administration conditions which more closely models treatment approaches for alcoholism in humans.

The goal for this study was to determine the effects of acute (1 day) versus chronic (10 days) treatment with combination of ondansetron and topiramate on ethanol's reinforcing effects as assessed in P rats responding for ethanol under a progressive-ratio (PR) schedule. The PR schedule is an established measure of the reinforcing effects of drugs of abuse (Richardson and Roberts, 1996; Stafford, LeSage, & Glowa, 1998). Low doses of each medication, which either do not affect (ondansetron; 0.001 mg/kg) or only modestly affect (topiramate; 10 mg/kg) alcohol-related behaviors on their own (Tomkins, Le, & Sellers, 1995; Lynch et al., 2011; Moore, Protzuk, Johnson, & Lynch 2013), were selected in an attempt to maximize their combined efficacy while minimizing potential side-effects. We hypothesized that this combination treatment, both acutely and over the course of chronic administration, would produce greater and less variable reductions in ethanol's reinforcing effects as compared to topiramate alone.

Methods

Animals and Housing

Male P rats (N=22) were obtained from the Indiana Alcohol Research Center's Animal Production core (Indianapolis, IN). The P line of rats has been selectively bred for high levels of ethanol intake and has been characterized by numerous studies as a valid animal model of alcohol abuse (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 7:00AM) throughout the course of the study. Animals were given 1 week to habituate prior to experiments and were 11–12 weeks old at the start of self-administration. Food and water were provided *ad libitum* with intake of each measured daily. Animal health was monitored daily and weights twice weekly by trained laboratory staff. All animal protocols were approved by the Animal Care and Use Committee at the University of Virginia.

Drugs

Ethanol solutions (10% v/v) were prepared from 190 proof absolute ethyl alcohol (Pharmco-Aaper, Brookfield, CT, USA) and diluted using tap water. Sucrose solutions were prepared as w/v in tap water. Sucrose and topiramate were obtained from Sigma-Aldrich (St. Louis, MO). Ondansetron was obtained from Glaxo Research Development. Treatments were dissolved in sterile water and physiological saline. The doses for topiramate (10 mg/kg, interperitoneal) was selected based on previous studies demonstrating its ability to modestly and selectivity reduce ethanol consumption on its own under a 2-bottle choice paradigm following acute administration (Lynch et al., 2011). The dose of ondansetron (0.001 mg/kg, IP) was selected based on previous work *with P rats*, showing that although not effective on its own, when combined with the 10 mg/kg dose of topiramate, it effectively reduced ethanol consumption (Lynch et al., 2011).

Sucrose-fade procedure

Animals were moved daily to self-administration chambers within sound-attenuating boxes (Med Associates, St Albans, VT, USA) for testing sessions. Food and water were not available during these testing sessions. These chambers contained a house light (4.76 W) that was illuminated during the session, and 2 levers; a right lever (water-associated lever) and a left lever (sucrose/ethanol-associated lever). Above each lever, there was a light (4.76W) that was illuminated during liquid deliveries. Rats were trained to self-administer ethanol deliveries using a sucrose-fade procedure previously described (Samson, Tolliver, Lumeng, and Li, 1989). Briefly, during 60 minute sessions, responding was reinforced under a fixed-ratio 1 (FR1) schedule, in which each response on the right or left lever led to a delivery of 0.1 ml liquid. During the initial training sessions, responses on the left (active) lever were reinforced with 10% sucrose with ethanol faded into the sucrose solution in 2% increments when animals reached specific criteria (0% variation in deliveries and 60% or greater preference for the sucrose/ethanol vs. water lever). Once the solution reached 10% sucrose/10% alcohol, the sucrose was faded out in 2% increments using the same criteria until animals were responding for 10% alcohol only. Responses on the right (control) lever activated a second pump and resulted in a delivery of water. Rats were maintained on 10% ethanol until a stable baseline was established (defined as less than 20% variability in the number of deliveries between sessions).

Effect of acute and chronic topiramate alone and in combination with ondansetron on ethanol's reinforcing effects

Once responding stabilized under these FR1 conditions, animals were placed on a PR schedule to measure ethanol's reinforcing effects. With this schedule, animals must respond for ethanol (and water) at higher levels for each subsequent delivery of ethanol in the following steps: 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, etc. Sessions ended after 30 minutes without a response on either lever, typically between 45–75 minutes. Ethanol's reinforcing effects were assessed daily and defined by the breakpoint, or the last ratio completed (the number of deliveries obtained within each session). The effect of acute topiramate alone or combined with ondansetron on ethanol's reinforcing effects was examined on a stable baseline using a between-subject design, with animals randomly

assigned to one of the three treatment groups. On test days, a single treatment of topiramate (10 mg/kg) or a combination of topiramate and ondansetron (10 mg/kg topiramate/0.001 mg/kg ondansetron), or an equal volume of saline was administered intraperitoneally 30 minutes prior to the start of the daily operant session. Chronic topiramate or combination treatment was examined at least 5 days after acute treatment, after baseline was re-established. Treatments occurred for 10 successive days, 30 minutes prior to the start of daily operant sessions.

Statistical Analysis

In order to equate baseline levels of PR responding for ethanol between the treatment groups, all analyses were conducted on percent change from baseline values (baseline was defined as the average number of deliveries on the three days preceding treatment). Given our previous findings showing persistent effects of these medications after acute treatment (Lynch et al., 2011), their effects were examined by comparing the percent change from baseline on the day of treatment and three days post-treatment using a repeated-measures analysis of variance (ANOVA). The effects of chronic treatment were examined by comparing the percent change from baseline number of ethanol deliveries between each of the treatment groups on the ten days of chronic treatment. To further analyze differences between early vs. late phases of chronic administration we compared percent change from baseline number of ethanol deliveries between each of the treatment groups for the first 5 days and the last 5 days. Following a significant overall effect post hoc comparisons with vehicle were made using Dunnett's t-test. Similar analyses were used to examine treatment effects on food intake in the home cage, as well as water deliveries obtained during testing sessions. However, since brain tissue was harvested following the last treatment day, food intake data were collected only on treatment days 1–9. Statistical analyses were performed using SPSS (version 20) with 0.05 as the alpha level for statistical significance for all tests.

Results

Effects of acute topiramate alone and in combination with ondansetron on ethanol's reinforcing effects

Acute treatment of both topiramate alone and the combination of topiramate (10 mg/kg) and ondansetron (0.001 mg/kg) reduced PR responding for ethanol (see Figure 1). Although there was no significant difference between the treatment groups at baseline ($p > 0.05$; See Table 1), an analysis of the percent change from baseline levels of ethanol deliveries over the four day testing period revealed significant overall effects of day, $F(3,54) = 4.27$, $p < 0.05$, and treatment $F(2,18) = 10.04$, $p < 0.05$. Post-hoc comparison with vehicle revealed a significant decrease with topiramate alone and the combination of topiramate and ondansetron (p 's < 0.05), indicating persistent decreases in ethanol's reinforcing effects after acute treatment with both compounds. Subsequent comparison to vehicle within each of the testing days revealed significant effects of topiramate alone and the combination on the day of treatment (p 's < 0.05). These effects persisted throughout post-treatment days 1–2 (p 's < 0.05), but returned to baseline by post-treatment day 3 ($p > 0.05$). Comparison of the combination treatment to topiramate alone on each of the four testing days revealed no significant differences. Thus, topiramate alone and in combination with ondansetron

persistently reduced the reinforcing effects of ethanol, although the combination was no more efficacious than topiramate alone.

Effects of chronic topiramate alone and in combination with ondansetron on ethanol's reinforcing effects

Both topiramate alone and the combination decreased PR responding for ethanol during the initial chronic treatment phase (first 5 days); however, with the combination, but not with topiramate alone, this reduction was maintained throughout the 10-day treatment period (see Figure 2). Although there was no significant differences between the treatment groups at baseline ($p > 0.05$; Table 1), an analysis of percent change from baseline number of ethanol deliveries over the ten day testing period revealed significant overall effects of day, $F(1,18) = 8.38$, $p < 0.05$, and treatment, $F(2,18) = 3.91$, $p < 0.05$. Post-hoc comparison with vehicle revealed a significant decrease with the combination of topiramate and ondansetron ($p < 0.05$) and a trend for a decrease with topiramate alone ($p = 0.08$) indicating persistent decreases in ethanol's reinforcing effects with these treatments. An analysis of the effects of topiramate alone and in combination with ondansetron during early versus later phases of chronic administration revealed significant effects of phase, $F(1,18) = 9.26$, $p < 0.05$, and treatment $F(2,18) = 3.90$, $p < 0.05$. Although no significant effect of treatment was observed on the first day of administration (p 's > 0.05), an analysis within the first five days revealed significant reductions in PR responding for ethanol for both topiramate alone and the combination compared to vehicle (p 's < 0.05). An analysis of the last 5 days of chronic treatment revealed a significant decrease with the combination ($p < 0.05$), but not topiramate alone. Thus, both topiramate and the combination reduced ethanol's effects in the early phase of chronic administration, but only the combination maintained this reduction throughout the chronic treatment period.

Side effects of topiramate and ondansetron: PR responding for water deliveries and food intake in the home cage

No effects of acute topiramate or combination treatment were seen on food consumption in the home cage or PR responding for water during the operant testing sessions (see Figure 3a–b). Water deliveries and food consumption in the home cage at baseline were not different between any of the treatment groups ($p > 0.05$; Table 1). An analysis of the percent change from baseline food consumption across the four day testing period (i.e. acute treatment day and three post-treatment sessions) revealed a significant effect of day, $F(3,54) = 5.54$, $p < 0.05$, but no significant effect of treatment, and post-hoc comparisons showed no difference from vehicle (p 's > 0.05 ; see Figure 3a). An analysis of percent change on just the day of acute administration also revealed no effect of treatment on food consumption despite a nearly 20% reduction in food consumption on the day of topiramate and combination treatment ($p > 0.05$). A comparison of percent change from baseline water deliveries obtained across the 4-day testing period revealed no significant effects of day or treatment (p 's > 0.05 ; see Figure 3b). An analysis of percent change on just the day of acute administration also revealed no effect of treatment on water deliveries ($p > 0.05$).

Similarly, no effects of chronic topiramate or combination treatment were seen on food consumption in the home cage or PR responding for water (see Figure 3c–d). Water

deliveries and food consumption in the home cage at baseline were not different between any of the treatment groups ($p > 0.05$; Table 1). An analysis of percent change from baseline food consumption across the 10-day testing period revealed no significant effects of day or treatment (p 's > 0.05 ; see Figure 3c). An analysis of percent change from baseline water deliveries obtained across the 10-day treatment period revealed no significant effects of day or treatment (p 's > 0.05 ; see Figure 3d).

Discussion

In this study, we examined the effects of a low dose combination of topiramate and ondansetron, medications shown to be effective in treating alcohol-dependent humans when administered as single agents on ethanol's reinforcing effects in rats. We determined this combination's effects acutely as well as during chronic administration which more closely models treatment approaches used in alcohol-dependent humans. Our results demonstrate that both topiramate alone and the combination of topiramate and ondansetron reduced ethanol's reinforcing effects after acute administration, although the combination was no more efficacious than topiramate alone. In contrast, after chronic administration, while both topiramate alone and the combination effectively reduced ethanol's reinforcing effects during the initial treatment phase, with the combination, but not topiramate alone, this reduction was maintained throughout the 10-day treatment period. These results suggest an advantage of the combination over topiramate alone at producing a sustained reduction in ethanol's reinforcing effects following prolonged chronic treatment.

Each of these medications on their own has been shown to have beneficial effects on AUDs in humans. Similar to our findings, this combination was shown to reduce ethanol consumption and relapse behavior after acute administration (Lynch et al., 2011). While this was the first study to determine the effects of this combination during chronic administration, topiramate alone had previously been tested in a chronic paradigm, with results similar to our study. Specifically, Hargreaves & McGregor (2007) also reported that while topiramate reduced responding for ethanol during the initial chronic treatment phase, this effect disappeared after repeated administrations. Surprisingly, we did not see an effect of topiramate alone on ethanol's reinforcing effects on the first day of chronic treatment. On this first day, of the 7 animals treated with topiramate, 2 reduced their responding, 3 maintained the same responding, and 2 animals slightly increased their responding. This data, as well as other data collected using this dose of topiramate (Hargreaves & McGregor, 2007; Moore et al., 2013), further demonstrates the variability in efficacy after the initial acute treatment. While the combination treatment also appeared to be less robust on the first day of chronic administration as compared to during acute administration, it is notable that the combination reduced the variability in responding observed with topiramate alone and had sustained efficacy.

Other combination medications for the treatment of AUDs have also shown promise in both clinical and preclinical studies. Studies investigating ondansetron combined with naltrexone (an opioid antagonist) show that this combination reduced alcohol drinking in early-onset alcoholics compared to placebo (Ait-Daoud, Johnson, Prihoda, & Hargita, 2001), as well as ethanol drinking in mice and rats with limited access to alcohol (Le & Sellers, 1994). Recent

findings from our group show that acute treatment with a combination of topiramate and naltrexone reduced ethanol consumption and reinforcement (Moore et al., 2013). These studies, as well as the current findings, support combination medications for the treatment of AUDs. Additionally, a benefit of a combination approach is the ability to use low doses, which may be sub-optimal on their own, but are effective when combined. These low doses often produce fewer side effects, an effect demonstrated by the current study, where the combination treatment did not affect food consumption in the home cage or water deliveries obtained during the testing sessions.

Although topiramate alone initially reduced ethanol's reinforcing effects, with repeated administration, it was no longer effective. Similar findings are often seen in clinical trials where the patient is initially reducing drug use or abstaining, but then suddenly relapses (Kadden, Carbonari, Litt, Tonigan, & Zweben, 1998). These data lend support to the idea that while a treatment may be initially efficacious, its effects may change over time. This loss of medication efficacy could be a function of reduced ethanol intake, changes in neurobiology due to repeated treatments, or both. Serotonergic as well as GABAergic and glutamatergic systems are involved in relapse vulnerability in humans (Heinz et al., 2009) and rodent models (Lê & Shaham, 2002). Thus, a combination that targets each of these neurotransmitter systems may be more efficacious at maintaining low drug intake during this state. *It is also notable that after acute administration with topiramate and the combination, PR responding for ethanol is reduced for 2 days following treatment. While the mechanism for this persistent effect is not yet known, it may involve plastic changes in GABA/glutamate/serotonin/dopamine transmission.*

Limitations of the present study are that only one low-dose combination was tested and ondansetron was not tested alone. Although the doses tested were carefully selected in attempt to minimize side effects while maximizing the efficacy of the medications in combination, it is possible that higher doses would have been even more efficacious, and would have also maintained a low-side effect profile. It is also possible that ondansetron alone would have affected ethanol self-administration. While no effects were seen previously under acute treatment conditions (Tomkins, Lê, & Sellers, 1995; Lynch et al., 2011), or during initial periods of chronic treatment (5 days; Beardsley et al., 1994), it is possible that effects would have been apparent following prolonged chronic administration. This is an important point for future studies, particularly given that the differences we observed in the present study between topiramate alone and the combination became apparent following prolonged chronic treatment. More research is also needed to understand the biological mechanism for how these two medications interact to prolong the beneficial effects throughout chronic administration (e.g., signaling pathways, ethanol metabolism and pharmacokinetics).

The present study focused on the effect of this combination in male rats only. While sex differences have been extensively explored in other drugs of abuse, historically, alcohol studies focus on groups of rats of the same sex. Males have been the traditional model for this; however, females are also used often, as female rats typically consume high levels of ethanol without extensive training (Lancaster, 1994). Studies involving pharmacotherapies for alcohol use disorders are largely influenced by the neurobiology of alcohol use

(rewarding effects, consequences of use, etc.), which differs between males and females (Blanchard & Glick, 1995; Lynch, Roth, & Carroll, 2002). Unfortunately, sex differences in alcohol studies have received very little attention in the past, likely due to the notion that the animal data do not mimic human data. However, it is important to examine sex differences in both ethanol use and response to pharmacological treatments for AUDs, as women make up a large part of humans with these disorders. Studies are underway to address this research gap.

In summary, these findings support the hypothesis that the combination treatment would be more efficacious than topiramate alone under chronic treatment conditions. Both topiramate and the combination effectively reduced ethanol's reinforcing effects acutely; however, under chronic administration, this effect persisted with the combination, but not topiramate alone. These findings showing that the combination produces persistent reductions in the reinforcing effects of ethanol throughout chronic treatment support the combination of topiramate and ondansetron as a promising new treatment for AUDs.

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Figure 1.

Acute treatment with the combination of topiramate and ondansetron significantly decreases ethanol's reinforcing effects. (a) Data is plotted as mean ($\pm$ SEM) of the percent change from baseline ethanol deliveries obtained on the day of treatment (0), and for 3 days thereafter (1,2,3). An asterisk (*) denotes a significant decrease from baseline when compared to vehicle ($p < 0.05$). Each data point represents an N of between 6 and 8. Veh = Vehicle; Top = Topiramate-10 mg/kg; Top + Ond = Topiramate 10 mg/kg and Ondansetron 0.001 mg/kg.

Figure 2.

Chronic treatment with the combination of topiramate and ondansetron decreases ethanol's reinforcing effects. (a) Data is plotted as mean ($\pm$ SEM) of the percent change from baseline ethanol deliveries obtained on each of the 10 days of treatment. (b) Decreases in ethanol deliveries obtained are shown as average percent change from baseline for the first five treatment days and the last 5 treatment days. An asterisk (*) denotes a significant decrease from baseline when compared to vehicle ($p < 0.05$). Each data point represents an N of between 6 and 8. Veh = Vehicle; 10-Top = Topiramate-10 mg/kg; 10-Top + Ond = Topiramate 10 mg/kg and Ondansetron 0.001 mg/kg.

Figure 3.

Acute and chronic treatment with the combination of topiramate and ondansetron did not affect food consumption or water deliveries obtained. (a) Food intake data is plotted as mean ($\pm$ SEM) of the percent change from baseline food intake on the day of acute treatment (0), and for 3 days thereafter (1,2,3). (b) Water deliveries data is plotted as mean ($\pm$ SEM) of the a percent change from baseline water deliveries obtained on the day of acute treatment (0), and for 3 days thereafter (1,2,3). (c) Food intake data is plotted as mean ($\pm$ SEM) of the a percent change from baseline food intake on the first 9 treatment days. (d) Water deliveries data is plotted as mean ($\pm$ SEM) of the a percent change from baseline water deliveries obtained for each of the 10 treatment days. Each data point represents an N of between 6 and 8. Veh = Vehicle; 10-Top = Topiramate-10 mg/kg; 10-Top + Ond = Topiramate 10 mg/kg and Ondansetron 0.001 mg/kg.

Table 1

Food consumption in the home cage and water deliveries obtained during testing sessions

		Acute		Chronic		
		Baseline	Tx Day	Baseline	Days 1–5	Days 6–10
Ethanol Deliveries	Vehicle	9.7 (0.7)	9.4 (1.0)	9.6 (0.3)	9.6 (0.4)	10.0 (0.3)
	10-Top	11.1 (1.6)	8.0 (0.9)*	10.0 (0.6)	8.9(0.8)*	9.6 (1.3)
	10-Top +Ond	10.9 (0.7)	7.5 (2.6)*	11.1 (0.8)	9.4 (0.7)*	8.8 (0.9)*
Food Consumption (g)	Vehicle	20.4 (1.3)	19.1 (1.6)	20.4 (1.0)	19.9 (0.7)	20.2 (0.7)
	10-Top	21.8 (1.9)	17.5 (2.3)	21.6 (1.0)	20.7 (1.3)	20.3 (0.9)
	10-Top +Ond	19.5 (1.9)	16.8 (2.3)	20.5 (1.5)	18.8 (1.6)	19.6 (1.5)
Water Deliveries	Vehicle	4.5 (0.5)	3.4 (0.7)	3.0 (0.3)	2.6 (0.4)	2.9 (0.4)
	10-Top	4.2 (1.2)	2.7 (0.3)	4.7 (1.0)	4.4 (0.9)	4.6 (1.0)
	10-Top +Ond	4.4 (0.5)	3.0 (0.9)	4.2 (0.6)	3.6 (0.2)	3.2 (0.4)

Note. Data are presented as mean (SEM) at baseline and on the day of treatment. An asterisk (*) denotes a significant decrease from baseline when compared to vehicle. 10-Top, Topiramate-10 mg/kg; 10-Top+Ond, Topiramate 10 mg/kg and Ondansetron 0.001 mg/kg.