Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: A 12-week, randomized, placebo-controlled trial

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\textbf{A B S T R A C T}

\textbf{Background:} Initiation of a relapse prevention medication is crucial at the end of alcohol detoxification. This study aimed to examine the efficacy and safety of topiramate for alcoholism in patients receiving a residential treatment program of alcohol detoxification and post-acute treatment.

\textbf{Methods:} This was a 12-week, randomized, double-blind, placebo-controlled trial of topiramate for alcoholism in patients receiving a residential treatment program. Individuals with DSM-IV alcohol dependence with minimal withdrawal were enrolled. Participants were randomly assigned to receive either 100–300 mg/day of topiramate or placebo. Primary outcomes were given as percentages of heavy drinking days and time to first day of heavy drinking. Other drinking outcomes, craving, and health-related quality of life were evaluated.

\textbf{Results:} A total of 106 participants were randomized to receive topiramate (\(n = 53\)) or placebo (\(n = 53\)). Twenty-eight participants of the topiramate group (52.8\%) and 25 participants of the placebo group (47.2\%) completed the study. Averaged over the trial period, there was no significant difference between groups on the mean percentages of heavy drinking days [1.96 (\(-1.62\) to \(5.54\)), \(p = .28\)]. Log rank survival analysis found no difference of time to first day of heavy drinking between topiramate and placebo groups (61.8 vs. 57.5 days, respectively; \(\chi^2 = 0.61, d.f. = 1, p = .81\)). Other secondary outcomes were not significantly different between groups.

\textbf{Conclusions:} By using a conservative model for data analysis, we could not detect the effectiveness of topiramate in this particular population. As the sensitivity analysis showed a trend of its benefit, further studies in larger sample sizes are still warranted.

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1. Introduction

Medications for alcohol relapse prevention are available but still not satisfactory. It is widely accepted that pharmacotherapy, in conjunction with psychosocial interventions, is a safe and effective measure for the relapse prevention of alcoholism. Food and Drug Administration (FDA)-approved agents, such as, disulfiram, acamprosate, and oral/extended-release naltrexone, can reduce alcohol consumption and increase abstinence rates. Recent data collected from the United States indicated that pharmacotherapy for drug and alcohol dependence has increased (Mark et al., 2009). Yet, the proportions of patients for whom these medications are accepted or prescribed are notably low. Approximately 85.8\% of patients treated with naltrexone may discontinue their medications within 6 months of treatment (Kranzler et al., 2008). Topiramate is effective in reducing drinking days, heavy drinking days, and drinks per day (Johnson et al., 2003, 2007). In a recent randomized-controlled trial, it was effective in increasing time to first relapse, abstinence duration, and percentage of abstainers (Baltieri et al., 2008). In this later study, only topiramate but not naltrexone was superior to placebo in those respects.

The end of alcohol detoxification is a crucial time for initiating a relapse prevention program. A guideline suggests that relapse prevention medications should always be considered after detoxification (p. 378) (American Psychiatric Association, 2006). Initiations
of disulfiram require (Barth and Malcolm, 2010) and acamprosate may require a period of abstinence.

A residential treatment program, including inpatient detoxification and post-acute care, may be needed for some individuals with alcoholism. Inpatient detoxification is preferred for those with severe somatic, psychiatric, or social disorders; those lacking social support; no occupational integration; unstable housing conditions; and repeated relapses during outpatient treatment (Rosseger et al., 2009). Post-acute care is an opportunity for establishing long-term stability and relapse prevention by providing interventions designed to limit physical as well as psychological impairment. Although outpatient post-acute treatment is preferred in many countries, as a part of residential treatment program, inpatient post-acute treatment is still widely accepted in some countries, e.g., Thailand.

In all three randomized, placebo-controlled trials of topiramate for alcoholism, no patients recently receiving residential treatment programs were enrolled into the studies (Baltieri et al., 2008; Johnson et al., 2003, 2007). Two of them did not require detoxification or abstinence prior to the enrollment (Johnson et al., 2003, 2007). Because some alcoholic patients receiving a residential treatment program also need a prophylactic medication after their discharges, we proposed to carry out a randomized-controlled trial to examine the efficacy and safety of topiramate in this population.

2. Methods

2.1. Design

A 12-week, parallel, double-blind, randomized, placebo-controlled trial was performed to determine the efficacy of topiramate in reducing drinking, craving, and heavy drinking, as well as promoting abstinence duration and health-related quality of life (HRQOL), in alcohol-dependent patients recently receiving a residential treatment program. We planned to initiate topiramate when an alcoholic patient was almost discharged from his/her residential treatment program and continued giving the medication during the follow-up. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study protocol was approved by the Ethics Committee for Human Research or Institutional Review Board of each site. Informed consent was obtained from the participants after the study details had been fully explained.

2.2. Participants

Between June 1, 2010 and November 30, 2010, participants were recruited at 3 sites in Chiang Mai, Thailand, including a psychiatric inpatient unit of a university hospital, a mental health hospital, and a drug dependence treatment center. These settings were the main resources of 2- to 4-week residential treatment programs for Chiang Mai people with alcohol-related disorders. Most patients receiving these residential programs are those meeting the above-mentioned admission criteria described by Rosseger et al. (2009).

We screened residential patients with DSM-IV alcohol dependence by using the Mini International Neuropsychiatric Interview (MINI; Sheenan et al., 1998). The inclusion criteria were: (i) aged between 18 and 60 years old; (ii) >1 week of ≥35 standard drinks in men or ≥28 standard drinks in women, during the 4-week period prior to admission; (iii) an Alcohol Use Disorders Identification Test (AUDIT) score of 8 or more (Bohn et al., 1995); (iv) mild or no alcohol withdrawal [revisted Clinical Institute Withdrawal Assessment of Alcohol Scale (CIAWA-Ar score ≤ 10; CIAWA-Ar delirium score < 1 and CIAWA-Ar score for psychotic symptoms < 1; (v) likely to be discharged within 14 days; (vi) a body mass index ≥ 18 kg/m²; and (vii) intention to decrease or stop drinking (Sullivan et al., 1989).

Exclusion criteria included: (i) previous or current cognitive disorder, schizophrenia and other psychotic disorders, bipolar disorder, or antisocial personality disorder; (ii) other substance dependence, except nicotine and caffeine dependence, during six months prior to the enrollment; (iii) being treated with antipsychotics, mood stabilizers, anticonvulsants, opioid analgesics, systemic steroids, carbinoic anhydride inhibitors, hydrochlorothiazide, metformin, pioglitazone, or disulfiram; (iv) risk of suicide, drug or alcohol use or any use other than topiramate for at least four weeks prior to the enrollment (MINI module C suicidality ≥ 8); (v) physical illnesses, including narrow angle glaucoma, renal impairment, urinary stone, and epilepsy; (vi) unstable medical conditions; (vii) pregnancy and breast feeding; and (viii) receiving medication for 14 days or longer while being inpatients. Apart from the suicidality and pregnancy, these exclusion conditions were assessed using medical record, clinical interview, and physical examination. We excluded antisocial personality disorder because this condition can be disruptive in inpatient units (Black, 2006). Inpatients with this disorder comorbidity may need inpatient treatment programs slightly different from others.

Those who met inclusion criteria and unmet exclusion criteria were enrolled in the study and started receiving topiramate on the next day after the enrolment, which was before being discharged from the residential treatment settings. They continued the medication during outpatient follow-up. Because both naltrexone and acamprosate are not available in Thailand, none of them had ever treated with these medications. During the study, participants suffering from a severe relapse or any cause could be hospitalized. They could continue their participation as long as they had remained on the medications and were hospitalized fewer than 14 days.

2.3. Assessment and outcome measures

The Mini International Neuropsychiatric Interview (MINI) was used to confirm the diagnosis of DSM-IV alcohol dependence. All efficacy and safety outcomes were measured at baseline (week 0), week 4, week 8, and week 12. At each assessment, drinking was evaluated during the 28 days prior to the visit. At week 4, days for evaluation were twenty-eight days minus days of medication treatment during admission. At week 8 and 12, days of evaluation were twenty-eight days minus days of rehospitalization, if any. Drinking characteristics were assessed using the timeline follow-back (Sobell and Sobell, 1992). An eleven-point Likert-type questionario (0 = none to 10 = very much) was used to assess the severity of alcohol craving. We used the visual analog technique as it is an ordinal scale simply measuring intensity of craving or desire. It is simple to understand; easy and cost-efficient to administer and score. In addition, it minimizes respondent burden and related risks of refusal (Berghvist and Rossiter, 2007; Sloan et al., 2002).

Heavy drinking days (numbers of days for which men consumed ≥5 standard drinks per day or women consumed ≥4 standard drinks per day divided by the number of study days) and time to first day of heavy drinking were primary outcomes. Time to first day of heavy drinking was defined as days to first heavy drinking day after the start of medication. Secondary drinking outcomes included patients with heavy drinking relapse, heavy drinking days, drinking days, drinking per day, of alcohol craving [from none (0) to very much (10)], and plasma gamma glutamyltransferase (GGT), a biomarker to provide a laboratory measure of drinking reduction.

HRQOL was measured using the Medical Outcomes Study Short Form 36-item questionnaire (SF-36). Thai version (Kongsakon and Silpakit, 2000; Ware and Sherbourne, 1992). The scores of 21 and 14 items were summed as physical component summary (PCS) and mental component summary (MCS), respectively (Ware et al., 1993).

Another six-point Likert-type questionario (0 = none to 5 = very severe) was used to assess five side effects commonly found in topiramate-treated patients, including paresthesias, taste perversion, poor appetite, impaired concentration, and pruritus (Johnson et al., 2007). Self-reported adverse events informed during the clinical interview were also recorded.

2.4. Randomization and blinding

A 50 mg tablet of topiramate with starch or identical capsules filled with starch alone were used. Topiramate and matching placebo capsules were provided by the Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University. The allocation ratio for being an intervention participant or a control was 1:1. Randomization was balanced using permuted blocks of six. Random allocation sequences were generated by the computer. A random number indicating intervention or control treatment was kept in an opaque and sealed envelope. The envelope was opened after the baseline assessment of each participant had been completed. The participants, care providers, and those assessing outcomes were blinded to the assigned treatment. At week 4, all participants were requested to guess whether they received active medication.

2.5. Procedure

The residential treatment program utilized in this study included an inpatient detoxification plus post-acute treatment. Post-acute treatment included 1–2 sessions of individual motivational enhancement therapy (MET), individual counseling for alcohol and drug use, group therapy, and family counseling. After discharge, participants received 2 or 3 sessions of individual MET. All MET sessions were given by trained psychologists or mental health nurses. Medical management was delivered by physicians at baseline, week 4, week 8, and week 12.

Topiramate was initiated before discharge from the residential treatment settings and continued during outpatient follow-up. The medication was initiated the next morning after enrollment and titrated at the dose-escalation schedule used in a previous study (Johnson et al., 2007). The titration was completed by scheduled increments in the number of topiramate tablets or an equivalent number of matching placebo tablets. To remain in the study, participants had to achieve a minimum study treatment dose of 100 mg/day or the placebo equivalent by week 3 (day 21). After that, the dose could be adjusted to between 100 and 300 mg/day, based on the best judgment of physicians and patients. From weeks 12 to 14, participants were tapered off their medications as a safety precaution.
2.6. Statistical analysis

The power calculation of the sample was based on the results of a previous 12-week, randomized controlled trial in which the difference of heavy drinking days’ percentages was 27.61 (SD = 37.98; Johnson et al., 2003). At a 2-sided significant level of .05, we determined that a sample size of 41 participants in each group would be needed to achieve 90% power to detect a significant difference between groups on heavy drinking days. To compensate for an expected 30% dropout rate by week 4, 53 participants were needed for each group.

A Friedman’s test was used to assess the change of heavy drinking days within groups. Mean differences between group on self-reported drinking and log GGT throughout the study period were calculated using multilevel mixed effect modeling for repeated measures adjusting for baseline values by entering treatment, time and baseline values as covariates. The mixed effect model allowed for random effects on treatment group and time. This assumed that there was a population effect for treatment and time, but varied between individuals. Data were assumed to be missed at random. Sensitivity analysis was done using multilevel fixed effect modeling. In both analysis, interaction between treatment group and time were also explored and tested using likelihood ratio test. The Student t-test (unpaired) was complementarily used for the completion analyses of the mean differences between groups on these outcomes. The difference of time to first day of heavy drinking between the topiramate and placebo groups was analyzed using the Kaplan–Meier method. The participant who was lost to follow-up was assumed to have experienced heavy drinking on the day after his/her last contact.

The between-group difference on the number of patients with heavy-drinking relapses was analyzed on an intention to treat analysis with the Fisher’s exact test. Based on the last observation carried forward method, the Student t-test was used for the between-group comparisons of alcohol craving and SF-36 scores.

The scores obtained from the questionnaire assessing five common side effects of topiramate were converted to no (score 0) or yes (score 1–5). Other adverse events were self-reported.

A p-value of .05 or less (two-tailed) was used to determine the statistical significance. All analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Sample characteristics

We screened 195 patients hospitalized at the sites. Of these, 106 participated in the study, and 53 each were randomly assigned to receive topiramate or placebo (Fig. 1). All participants were male (Table 1). This sample had a mean age of 41.5 (SD = 8.9) years old, and 47.2% of them were married. During four weeks prior to admission, their mean drinks per day were 15.4 (SD = 11.8) drinks. Mean ages at first drink and onset of alcohol use disorders were 16.9 (SD = 3.7) and 29.3 (SD = 8.7) years old, respectively. Their mean

### Table 1

Baseline demographics and psychopathological characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Topiramate (n=53)</th>
<th>Placebo (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53 (100%)</td>
<td>53 (100%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>22 (41.5%)</td>
<td>28 (52.8%)</td>
</tr>
<tr>
<td>Single</td>
<td>17 (32.1%)</td>
<td>12 (22.6%)</td>
</tr>
<tr>
<td>Divorce</td>
<td>11 (20.7%)</td>
<td>11 (20.7%)</td>
</tr>
<tr>
<td>Separated and widow</td>
<td>3 (5.7%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Beverage of choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White whisky (28–40% rich alcohol)</td>
<td>43 (81.1%)</td>
<td>40 (75.5%)</td>
</tr>
<tr>
<td>Colored whisky (40% malt alcohol)</td>
<td>4 (7.5%)</td>
<td>8 (15.1%)</td>
</tr>
<tr>
<td>Beer</td>
<td>3 (5.7%)</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (5.7%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Psychotropic comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>2 (3.8%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (1.9%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>2 (3.8%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (1.9%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>2 (3.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>4 (7.5%)</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Psychotropic medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>7 (13.2%)</td>
<td>7 (13.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.4 (8.4)</td>
<td>40.7 (9.3)</td>
</tr>
<tr>
<td>Year of education</td>
<td>8.2 (4.3)</td>
<td>8.9 (3.8)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.3 (23.7)</td>
<td>21.7 (3.9)</td>
</tr>
<tr>
<td>History of alcohol drinking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at 1st drink</td>
<td>16.6 (4.1)</td>
<td>17.2 (3.3)</td>
</tr>
<tr>
<td>Age at 1st drinking problem (age of alcoholism onset)</td>
<td>28.8 (7.3)</td>
<td>29.8 (10.0)</td>
</tr>
<tr>
<td>Age at 1st drinking treatment, years</td>
<td>38.1 (11.3)</td>
<td>37.3 (10.9)</td>
</tr>
<tr>
<td>No. of previous hospitalization</td>
<td>2.3 (2.0)</td>
<td>3.6 (4.4)</td>
</tr>
<tr>
<td>CIWA-Ar score</td>
<td>1.1 (1.2)</td>
<td>1.3 (1.8)</td>
</tr>
<tr>
<td>Duration of admission (days)</td>
<td>26.0 (9.8)</td>
<td>24.0 (11.0)</td>
</tr>
<tr>
<td>Duration of medication treatment during admission (days)</td>
<td>3.4 (4.6)</td>
<td>3.9 (4.6)</td>
</tr>
</tbody>
</table>

CIWA-Ar, revised Clinical Institute Withdrawal Assessment for Alcohol scale.

* No significant difference between groups for all comparisons.

![Diagram](image-url)

**Fig. 1.** Trial profile. Trial completer were participants who completed all 12 weeks of double-blind treatment.
number of hospitalizations for alcohol treatment was 3.0 (3.5). Seventy-eight participants (78.3%) preferred white whisky (28–40% alcohol), made from rice.

At baseline, there were no significant differences between groups as to socio-demographic and drinking characteristics (Tables 1 and 2). There was a trend that the mean number of previous hospitalizations due to alcohol-related disorders was smaller in the topiramate group [2.3 (SD = 2.0) for the topiramate group vs. 3.6 (SD = 4.4) for the placebo group]. The mean duration of hospitalization and mean duration of medication treatment during admission were not significantly different between groups.

3.2. Treatment retention and blinding assessment

Twenty-eight participants in the topiramate group (52.8%) and 25 participants in the placebo group (47.2%) completed the study. Six, 16, and 3 topiramate participants dropped out of the study at week 4, week 8, and week 12, respectively. Reasons for the discontinuation included loss to follow up (n = 18), rehospitalization longer than 14 days (n = 4), adverse events (n = 2), and noncompliance to medication (n = 1). For placebo group, 11, 8, and 9 participants dropped out of the study at week 4, week 8, and week 12, respectively. Reasons for placebo discontinuation were loss to follow up (n = 21), rehospitalization longer than 14 days (n = 2), adverse events (n = 2), noncompliance to medication (n = 2), and consent withdrawal (n = 1). One patient in the placebo group was rehospitalized due to alcohol-related problems. Because he had less than 14 days of admission, his data were included in the analysis.

All participants achieved the minimum topiramate dose of 100 mg/day or the placebo equivalent by week 3 (day 21). As planned, all patients were discharged within 14 days after the initiation of the study medications. At week 4, 39 (85%) topiramate- and 36 (90%) placebo-treated patients believed that they were receiving topiramate.

3.3. Drinking and HRQoL outcomes

Table 2 shows the topiramate doses, and outcomes at four time points. The mean doses of topiramate at week 4, 8, and 12 were 145.0 (SD = 15.0), 190.0 (SD = 20.0) and 260.0 (SD = 55.0) mg/day, respectively. Within group analyses, both the topiramate and placebo groups had a significant reduction in heavy drinking days (χ² = 127.9; d.f. = 3, p < .01 and χ² = 105.2; d.f. = 3, p < .01, respectively).

Averaged over the trial period, there was no significant difference between groups on the mean percentage of heavy drinking days [1.96 (–1.62 to 5.54), p = .28] (Table 3). Additional analysis using multilevel fixed effect modeling did not materially change these results, excluding there was a trend that the mean percentage of heavy drinking days in the topiramate group was lower than that of the placebo group [3.06 (–0.51 to 6.62), p = .09]. There was also no evidence for interactions between treatment effect and time (p’s > .05, results not shown). No significant difference of the mean was found on other self-reported drinking outcomes and log GGT (p’s > .05). Except for a trend of decreased heavy drinking days in the topiramate group at week 4, the completion analyses did not show any significant difference on other self-reported drinking outcomes and the log GGT at four time points (p’s > .05).

Log rank survival analysis found no difference of time to first day of heavy drinking between groups (χ² = 0.61; d.f. = 1; p = .81) (Fig. 2). On an intention-to-treat basis, the number of patients with heavy-drinking relapses, alcohol craving, SF-36 Physical score, and
SF-36 Mental score were not significantly different between groups (Table 4).

### 3.4. Adverse events

Two placebo patients dropped out of the study due to serious adverse events (delirium and death due to cardiac arrest). No serious adverse event found in the topiramate group. For the five common side effects of topiramate assessed by using the questionnaire, only paresthesia was significantly more common in the topiramate group ($p = .003$) (Table 5). Other self-reported side effects were uncommon in both groups.

### 4. Discussion

In patients about to be discharged from a residential care program, those receiving topiramate or placebo treatments both decreased their drinking drastically over this 12-week, randomized, placebo-controlled trial. Topiramate was well tolerated but might cause paresthesia.

Reduction in percentage of heavy drinking days was the primary outcome in the present and two previous randomized-controlled trials (Johnson et al., 2003, 2007). It was a secondary outcome in another randomized-controlled trial (Baltieri et al., 2008). All of these trials found the benefit of topiramate in this respect. By using a conservative analysis of multilevel mixed effect modeling, the present study did not find the significant superiority of topiramate. However, our sensitivity analysis using a fixed effect model found a trend of its benefit in reducing heavy drinking in alcoholic patients recently receiving residential treatment programs of alcohol detoxification and post-acute care. The benefits of topiramate on other drinking outcomes, e.g., time to first day of heavy drinking, drinks per day, drinks per drinking day, drinking days (as a reverse of abstinence days), GGT found in previous studies were not observed in the present one.

Based on previous findings, we prospectively and qualitatively assessed five common side effects of topiramate, including, paresthesias, taste perversion, poor appetite, impaired concentration, and pruritus. Of these, paresthesia was found to be more common in topiramate-treated patients.

On average, the topiramate and placebo groups had 26 and 24 days of residential treatment, respectively, and took the study medication on an average of 3–4 days before discharges.

The present sample differed from those in previous studies, and this difference might lead to the dissimilar findings. While all of the present participants received inpatient detoxification, alcohol detoxification was not needed prior to the enrolment of two previous trials (Johnson et al., 2003, 2007). Only one trial had one-week outpatient detoxification prior to the initiation of study medication (Baltieri et al., 2008). Compared to outpatient treatment, inpatient detoxification is assumed to benefit all patients because it allows efforts toward abstinence to be consolidated (Finney et al., 1996). A variety of psychosocial interventions were given during the post-acute treatment period of the present study. While the present participants received 3–5 sessions of the individual MET, two previous trials gave only brief behavioral treatment to enhance compliance to topiramate (Johnson et al., 2003, 2007). While the participants in this study needed residential care, the heavy drinking days in this sample were comparable to those in a previous study (Johnson et al., 2007). Although the present sample size is smaller than those of the first two RCTs, it is comparable to that of the last one (Baltieri et al., 2008).

Taken together with the positive findings in previous studies, it is possible that, as a part of residential treatment program, intensive psychosocial interventions are effective in reducing alcohol consumption. The addition of topiramate further increases this effectiveness but in a lesser extent than that found in outpatients receiving less intensive psychosocial treatment. The different results between previous studies and the present one may be also due to the placebo effect. In the present study, 85% of topiramate group and 90% of the placebo group believed that they had received topiramate. Patient’s beliefs and expectations about the outcome represent crucial factors in every medical treatment and influence therapy efficacy (Carlino et al., 2012).

There are some limitations of the present study. First, we did not assess the adherence to medications. Due to this serious limitation, we could not determine whether the lower effectiveness of topiramate found in this study was caused by nonadherence to treatment. Secondly, the sample size of this study is relatively small. For the power analysis of a mean difference, a sample size less than 60 may not be able to detect a medium or small effect size (Cohen, 1992). A type II error could not be ruled out for a nonsignificant difference between groups found in this study. Thirdly, the

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### Table 3

Mean difference between topiramate and placebo on drinking outcomes averaged over trial period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean difference between study groups ($95% CI$)</th>
<th>$p$ value</th>
<th>Mean difference between study groups ($95% CI$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Heavy drinking days</td>
<td>$1.96^* (-1.62$ to 5.54)</td>
<td>.28</td>
<td>$3.06^* (-0.51$ to 6.62)</td>
<td>.09</td>
</tr>
<tr>
<td>Drinks per day</td>
<td>$-0.21^* (-1.43$ to 1.02)</td>
<td>.74</td>
<td>$-0.20^* (-1.38$ to 0.98)</td>
<td>.74</td>
</tr>
<tr>
<td>Drink/drinking days</td>
<td>$-0.35^* (-1.86$ to 1.15)</td>
<td>.65</td>
<td>$-0.08^* (-1.62$ to 1.45)</td>
<td>.91</td>
</tr>
<tr>
<td>% Drinking days</td>
<td>$2.03^* (-1.66$ to 5.73)</td>
<td>.28</td>
<td>$2.70^* (-2.24$ to 7.65)</td>
<td>.28</td>
</tr>
<tr>
<td>Log Gamma-glutamyl transferase (U/L)</td>
<td>$-0.02^* (-0.13$ to 0.09)</td>
<td>.70</td>
<td>$-0.10^* (-0.27$ to 0.08)</td>
<td>.27</td>
</tr>
</tbody>
</table>

GGT = gamma-glutamyl transferase.

* Values were calculated using mix-effect multilevel modeling across the entire double blind period.
* Values were calculated using fixed-effect multilevel modeling across the entire double blind period.
* Number of observation 310, number of individuals 105, average number of observations per individual 3.0 (range 1–4), baseline values not available for one participant.
* Number of observation 346, number of individuals 105, average number of observations per individual 3.3 (range 1–4), baseline value not available for one participant.
* Number of observations 309, number of individual 106, average number of observations per 2.9 (range 1–4).

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**Fig. 2.** Survival curve of time to first day of heavy drinking for participants randomized to topiramate or placebo. Participants included were those who received study medication and returned for re-evaluation at week 4.
between patients with relapses, alcohol craving, and Rand 36-item Health Survey analyses).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Topiramate (n=53)</th>
<th>Placebo (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Mental</td>
<td>1.8 (2.1)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>SF-36 Physical</td>
<td>2.0 (2.1)</td>
<td>1.9 (2.0)</td>
</tr>
<tr>
<td>SF-36 Role Function</td>
<td>2.0 (2.0)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>SF-36 Social Function</td>
<td>1.7 (2.0)</td>
<td>1.8 (2.0)</td>
</tr>
<tr>
<td>SF-36 Emotional</td>
<td>2.0 (2.0)</td>
<td>2.0 (2.0)</td>
</tr>
</tbody>
</table>

All outcomes presented as mean (SD).

Some significant differences were observed in the rates of dropout between patients with relapses, alcohol craving, and Rand 36-item Health Survey analyses.

The number of dropouts was high in both groups. Whatever the reason for the study attrition, a high dropout rate can affect the validity of the results. Some experts take the view that high dropout rates are a flaw of RCTs (Hardon et al., 1996; Peduzzi et al., 2002). Finally, the generalization of present findings to other ethnic groups should be done with caution. While continual drinking is a common pattern of alcohol dependence in Thai men (Assanangkornchai et al., 2000), alcoholic patients in other ethnic groups may have different patterns of drinking.

Despite the above-mentioned limitations, this study contributes new data on the effectiveness of topiramate for alcoholic individuals recently receiving a residential treatment program of alcohol detoxification plus post-acute treatment. By using a conservative model for data analysis, we could not detect the effectiveness of topiramate in this particular population. As the sensitivity analysis showed a trend of its benefit, further studies in larger sample sizes are still warranted.

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Contributors

Surinporn and Manit designed the study and wrote the protocol. Kanok, Hathaihnonnanee and Apisak managed the literature searches and summary of previous related work. Surinporn, Manit and Chaisiri conducted the statistical analysis. Surinporn and Manit wrote the first draft, and were responsible for integrating all co-authors feedback of the manuscript. Surinporn, Manit and Chaisiri were responsible for revision of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Srisurapanont have received honoraria, consultancy fees, research grants, and/or travel reimbursement from AstraZeneca, GlaxoSmithKline, Pfizer, Janssen-Cilag, Johnson & Johnson.
Lundbeck, Thai-Otsuka, Sanofi-Aventis, and Servier. All other authors declare that they have no conflicts of interest.

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