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

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ABSTRACT

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.
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.
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.
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.

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

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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 (Rossegger 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 Rossegger et al. (2009).

We screened residential patients with DSM-IV alcohol dependence by using the Mini International Neuropsychiatric Interview (MINI; Sheehan 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 [revised Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar score ≤ 10; CIWA-Ar delirium score ≤ 1 and CIWA-Ar score for psychotic symptoms ≤ 1; (v) likely to be discharged within 14 days; (vi) a body mass index ≥ 18 kg/m^2; 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, carbonic anhydrase inhibitors, hydrochlorothiazide, metformin, pioglitazone, or disulfiram; (iv) risk of suicide, during 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 questionnaire (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 (Bergkvist 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 relapses, drinking days, drinks per day, drinks per drinking day, 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 questionnaire (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 medication 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.