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Low-dose topiramate in alcohol dependence: a single-blind, placebo- controlled study

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Abstract

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Conclusion: Despite the small sample size and the short follow-up period, the present placebo-controlled study demonstrated the potential usefulness of topiramate, even when administered at a dose of 100 mg/day, for the treatment of detoxified alcohol-dependent subjects, confirming results from previous studies testing higher doses of topiramate.

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Introduction

Alcoholism and alcohol abuse are a worldwide public health concern causing significant morbidity and mortality[1]. Disulfiram, naltrexone and acamprosate have been approved for the treatment of alcohol dependence. However, their efficacy is limited and a significant number of subjects is treatment-resistant[2]. Furthermore, no single drug has been found to be effective in every case, and this is possibly linked to the multifactorial nature of the aetiology of alcoholism. Nalmefene has been recently approved in Europe for the treatment of alcohol dependence, but its long term effects on relapse prevention need to be further confirmed.

Several anticonvulsants have been shown to be effective for the prevention of alcohol relapse[3,4,5,6,7]. Although the FDA has not approved these drugs for the treatment of alcohol use disorders yet, there is growing evidence in literature supporting their use. Some, i.e. topiramate, are currently deemed to be promising anti-craving substances[8,9].

Alcohol dependence treatment comprises two phases: the withdrawal phase and the relapse prevention phase. During the latter, management of craving is crucial. The use of topiramate and anticonvulsants in general is safe and effective in both phases. The efficacy

of anticonvulsants in preventing epileptic seizures during alcohol withdrawal is, in fact, well-established; furthermore, they are considered to interact with the reward system[8]. Moreover, the efficacy of some anticonvulsants in treating psychiatric symptoms in substance use disorder patients[10,11,12] is also relevant, given the high number of alcohol-dependent subjects presenting a dual diagnosis[13].

Topiramate, a sulfamate-substituted analogous of fructose-1,6-diphosphate, is a potent anti-epileptic[14] with strong neuroprotective properties[15,16]. In treating alcohol dependence Johnson et al. proposed a neuropharmacological model by which topiramate decreases alcohol reinforcement and the propensity to drink[17,18]. These data have been confirmed by different studies in different settings[19,20,21]. According to this hypothesis, topiramate would be expected to suppress both acute and chronic alcohol consumption. This dual action of topiramate is thought to comprise an initial decrease in dopamine in the nucleus accumbens (NAcc) in response to alcohol use, leading to a subsequent reduction of its rewarding/reinforcing potential. This mechanism is exerted by the facilitation of the $GABA_A$-mediated inhibitory impulses, which is a peculiar action of topiramate. In chronic alcoholism, characterized by VTA-DA hypofunction, one must drink more heavily in order to stabilize the system and obtain good levels of reinforcement. On the other hand, if a chronic drinker were to discontinue alcohol consumption abruptly, the consequent "rebound" in dopaminergic neuronal activity could trigger drinking. Topiramate is thought to restore VTA-GABA neuronal activity, and, consequently, normalize VTA-DA hypofunction.

Topiramate has a linear profile across a wide range of doses, with a bioavailability of at least 80%. In addition, its interaction with other psychotropic drugs is scarce, though it

may worsen sedation and central nervous system depression, if taken with barbiturates, benzodiazepines, opiates and alcohol itself[9].

The adverse event profile of topiramate is favourable; symptoms are generally either mild or moderate. Common adverse events include: paraesthesia, anorexia, taste perversion, lack of concentration, memory impairment (including world-naming), psychomotor disturbance, and general cognitive impairment, which can be observed in 10% of individuals taking topiramate[22]. The occurrence of topiramate-induced adverse events increases if high initial doses are given or if titration to 300 mg/day is too rapid[9]. Cognitive impairment is particularly relevant for alcohol-dependent patients, who generally present with reduced cognitive performance[23,24]. The use of low doses of topiramate is, therefore, particularly promising in these patients, as reported in an open-label study in which add-on topiramate reduced craving in alcohol-dependent detoxified subjects[25].

The aim of the present study was to assess the efficacy and tolerability profile of low-dose topiramate for relapse prevention. Primary outcome measures included: abstinence by the end of the study period, number of alcohol drinking days, daily alcohol consumption. Craving reduction, improvement of psychiatric symptoms, and assessment of safety parameters were secondary endpoints.

Methods

Subjects

Sixty-four subjects (M/F 4/1; mean age 46.36 ± 11.8; mean daily drinks 8.5 ± 3.5; mean years of addiction 16.8 ± 6.7) with a history of alcohol use disorders lasting at least three years, daily alcohol intake of at least 6 units (1 drink= 12 grams of absolute alcohol), and currently meeting clinical criteria for Alcohol Dependence (DSM-IV-TR), were consecutively recruited at the Day-Hospital (outpatient unit) of Psychiatry and Drug Dependence of the University General Hospital "A. Gemelli" in Rome (n= 25) and among outpatients referring to the Alcohol use disorders unit of "Villa Silvia" at Senigallia (AN) (n=27). Patient enrolment started in August 2009 and was completed in August 2012. We included only patients who declared their commitment to the goal of total abstinence. Patients were assessed by attending psychiatrists using the Structured Clinical Interview for DSM-IV (SCID I; SCID II). Patients were excluded if they had a severe physical illness or evidence of severe mental disorders interfering with their cognitive abilities. Other exclusion criteria were: regular use of anticonvulsants, antidepressants or antipsychotics; pregnancy or lactation; a history of severe adverse reactions or well-known hypersensitivity to topiramate or benzodiazepines; previous treatment with topiramate.

The study was approved by the Institutional Review Board and national regulatory authorities in accordance with local requirements, and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964) and subsequent revisions. After receiving information on the drug (possible side effects and dosing rate), all patients (or their legal representatives) provided written informed consent prior to randomisation. Patients were free to leave the study at any time.

Procedures and assessments

All subjects underwent detoxification with diazepam for a period of 5 to 10 days, according to a validated protocol[6,12]. Twelve patients did not complete detoxification, and they were excluded from the study before randomisation procedures.

Following detoxification, 52 patients were randomised into two groups: 26 patients received 25 mg (per os, daily) of topiramate (TOP) during the first week, followed by 50 mg (per os, bid, daily) for the second week, and 100 mg (per os, bid, daily) for the remainder of the clinical trial; 26 patients received an initial dose of 1 tablet of placebo (PLA) then increased to 2 tablets (per os, bid, daily) over one week.

Randomization was performed using a common computer-generated system. Study personnel were unaware of the randomization sequence.

A flow diagram showing patient distribution according to treatment group is presented in **figure 1**. At the beginning of each week of treatment, the drug was supplied to both the patient and a selected family member. A schedule was also provided to control for compliance. Tablets were identical in appearance, and they were tested during the trial to confirm stability.

Throughout the entire study period, patients joined a supportive self-help group held by counsellors and psychologists twice a week. Random assignment was stratified according to the presence of a comorbid psychiatric diagnosis to ensure a relative balance in the overall prevalence of dual diagnosis among groups.

Subjects were assessed at the beginning (T0) and at the end of treatment (6 weeks, T1). The drug was gradually discontinued over a period of seven days after the last

assessment. The study was a single-blind design. However, at different times, assessment was carried out by the same investigator, who was unaware of which drug was being administered to patients.

Withdrawal symptomatology was assessed by the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)[26], whereas the intensity of alcohol craving was evaluated using a 10-cm Visual Analogue Scale (VAS)[27] and the Italian version of the Obsessive and Compulsive Drinking Scale (OCDS)[28]. Psychiatric symptomatology was evaluated with the Symptom Check List 90 Revised (SCL-90-R)[29]. Effectiveness measures included the Quality of Life (QoL) Index[30].

Abstinence from alcohol was determined based on self-evaluation measures and a family member interview. Abstinence was confirmed by performing blood alcohol tests at each outpatient follow-up visit (patients were tested twice a week after the group therapy session), by measuring alcohol abuse hepatic indices (aspartate aminotranferase (AST), alanine aminotranferase (ALT), gamma glutamyl-tranpeptidase (GGT)), and mean cellular volume (MCV) at the end of the study. Toxicological urinalysis was performed at each outpatient control in order to identify polysubstance abuse. Subjects were strongly advised against using drugs that could potentially influence craving for alcohol[31,32]. Blood alcohol tests and urinalysis were performed twelve times (twice per week, for six weeks) for those patients concluding the study procedures.

Primary study endpoints were maintenance of abstinence and relapse prevention. Drinking any alcohol marked the end of abstinence. Relapse was defined as drinking either five (four for women) or more standard drinks on a single occasion, or drinking on five or more days a week. This definition has been referred to for research purposes in different

studies[33,34]. Secondary study endpoints included: number of abstinent days, average daily alcohol consumption, retention in treatment, and reduction of alcohol craving. A drink is defined as 12 grams of absolute alcohol, roughly corresponding to half a pint of beer, a glass of wine, or a single (25ml) measure of spirit.

Safety parameters were monitored through ECG, urinalysis, haematological and clinical chemical analyses of blood samples at the start and at the end of the study.

Each patient was informed that relapse, non-compliance, or the onset of any severe side effects would lead to exclusion from the trial. However, patients were free to leave the study at any time.

Statistical analysis

Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients who took at least one dose of study medication.

Student's t- and Chi-square tests were employed in order to compare socio-demographic and clinical data with OCDS, VAS, SCL-90-R, QoL and CIWA-Ar scores to verify the presence of significant changes during the time period considered (T0-T1). Between-groups comparison (TOP vs. PLA) was performed using Student's t test to compare the mean difference between baseline and T1 scores.

Logistic regression analysis was employed to verify which variable most influenced outcome in terms of number of patients remaining abstinent at the end of the study.

Alcohol abuse indices were compared between groups and in different moments by means of the Chi-square test (abstinent and relapsed patients) and the Student's t-test (days of abstinence, days in treatment and drinking days).

Results

Patients and disposition

A total of 80 patients were initially screened; 18 were then excluded from the study, leaving 62 patients (38 males and 24 females). Reasons for exclusion were represented by: not fulfilment of the diagnosis of Alcohol Dependence according to DSM-IV-TR (8); regular use of anticonvulsants (2), antidepressants (4), antipsychotics (3), or previous treatment with topiramate (1). No significant differences were observed as to baseline characteristics between patients excluded from the study and those who were included in the study. Ten patients were excluded during the detoxification phase (9 for drop-out; 1 for the onset of suicidal thoughts and psychotic symptoms) and the final study sample consisted of 52 patients (32 males and 16 females). Of these, 26 were treated with topiramate and 26 with placebo (see **Figure 1**).

No statistically significant differences were found between patients assigned to topiramate and patients treated with placebo with respect to age, gender, education, marital status, employment, craving scores (OCDS; VAS), withdrawal scores (CIWA-Ar), baseline psychiatric symptomatology (SCL-90-R, GSI-Index), use of other substances, DSM IV-TR Axis I and II comorbidity. The characteristics of the sample are reported in **Table 1**.

Patients with polysubstance abuse and dual diagnosis were equally distributed in the two samples. Additional axis I diagnoses included: mood disorders (TOP=4; PLA=7), anxiety disorders (TOP=5; PLA=7), impulse control disorders (TOP=1), and eating disorders (PLA=1). Additional axis II diagnosis were Borderline (TOP=3; PLA=2), Antisocial (TOP=1; PLA=1), Avoidant (TOP=2; PLA=3), Histrionic (TOP=2; PLA=1), Passive-aggressive (TOP=1; PLA=1) and Schizoid (TOP=1) personality disorders.

Substance abuse, other than alcohol, comprised: cannabis (TOP=3; PLA=4), cocaine (TOP=2; PLA=3) or benzodiazepine abuse (TOP=3; PLA=4).

Cloninger Typology was represented by Type I (TOP=15; PLA=12) and Type II (TOP=11; PLA=14).

Efficacy

With respect to primary study endpoints (patients abstained and relapsed at T1), patients treated with topiramate were more likely to be abstinent ($p=0.001$; $X^2= 99.12$;) than controls. The number of relapsed patients, as confirmed by blood alcohol concentrations, was higher in the PLA group than in the TOP group (13 vs 5; $X^2= 98.82$; $p<0.001$). With respect to secondary endpoints, compared to the placebo group, at the end of treatment (T1) patients in the TOP group had: a) fewer days of drinking (9.5±8.3 vs 21.9±13.3; $t=2.77$; $p<0.05$); b) lower daily alcohol consumption (2.9±4.3 vs 5.8±4.1; $t=2.31$; $p<0.05$); c) more days of treatment (43.3±18.5 vs 29.4±12.2; $t=2.70$; $p<0.05$); and d) were more likely to be retained in treatment at T1 ($t=3.89$; $p<0.01$).

With respect to craving scores, the TOP group showed a significant reduction after 6 weeks of treatment (T1) on the VAS for craving ($t=2.88$; $p< 0.5$), on the OCDS ($t=4.91$; $p< 0.001$), and its subscores of OCDS obsessive ($t=4.86$; $p< 0.001$) and OCDS compulsive ($t=4.94$; $p< 0.001$). Likewise the PLA group showed a significant mean reduction in the VAS ($t=2.21$; $p< 0.5$), OCDS ($t=2.13$; $p< 0.05$) and its subscores of OCDS obsessive ($t=2.09$; $p< 0.05$) and OCDS compulsive ($t=2.17$; $p< 0.05$). Mean change from baseline in the two groups is described in **Figure 2**. A significant difference between groups was observed for OCDS scores ($t=3.01$; $p<0.01$), but not for VAS. Abstinent patients in both study groups showed significantly lower OCDS scores than relapsed patients, even after the exclusion of alcohol consumption items ($t=4.84$; $p<0.01$).

Withdrawal total scores as measured by the CIWA-Ar were significantly reduced in the TOP group ($t=4.89$; $p<0.001$) and in the PLA group ($t=2.12$; $p<0.05$). A significant difference between groups ($t=2.66$; $p<0.05$) was found in favour of the TOP group.

The SCL-90-R general index of "Positive Symptom Total" was significantly reduced after 6 weeks of treatment in both groups (TOP: Positive Symptom Total: $t=3.12$; $p<0.01$; PLA: Positive Symptom Total: $t=2.24$; $p<0.05$), whereas the subscales for "obsessive-compulsive" (**Figure 2**), "hostility", "anxiety" and "depression" showed significant reductions only in the TOP group ($t=2.86$; $p<0.01$; $t=2.88$; $p<0.05$; $t=2.21$; $p<0.05$; $t=2.29$; $p<0.05$). Scores (OCDS, VAS, SCL-90 GSI, CIWA-Ar) at baseline and at the end of treatment are reported in **Table 2**.

Patients in both groups showed a statistically significant improvement in scores on the Quality of Life scale (TOP: $t=2.09$; $p<0.05$; PLA: $t=2.19$; $p<0.05$), with no difference between groups.

The number of patients with dual diagnosis reporting a condition of total abstinence from alcohol at the end of the study was significantly higher (X^2= 98.12; p< 0.01) in the TOP group (6/10; 60%) compared to the PLA group (2/8; 25%).

Logistic regression analysis showed that the reduction of the OCDS scores was the most relevant factor (p<0.01) determining the maintenance of the alcohol-free condition in all randomised subjects. There was no indication of a separate factor specific to either the TOP or PLA group.

Safety and tolerability

Common adverse events (whether or not treatment-related) occurred in 7 patients of the TOP group and in 5 patients of the control group, with no statistically significant differences between TOP and controls. The overall rate of study discontinuation due to the occurrence of adverse events was 3.8 % (n=1) in the TOP group, and 3.8% (n=1) in the control group. Somnolence (n=3), dizziness (n=2), psychomotor retardation (n=1) were the adverse effects across the TOP group, with 1 case of dizziness being the event that led to patient withdrawal from the study. Somnolence (n=2), dizziness (n=1), nausea (n=1), and insomnia (n=1) were the adverse events across the control group, with nausea being the event that led to patient withdrawal from the study.

No clinically relevant difference between groups was observed in the mean change from baseline for any vital signs, ECGs, haematology, or clinical chemistry parameters. Comparing hepatic alcohol abuse indices before and after treatment, we found a significant decrease in GGT (p<0.01), AST (p<0.01) and ALT values (p<0.01) in all treatment groups,

with no significant difference between groups. This comparison between the reductions (Delta) in GGT, AST, and ALT showed a trend in favour of the group of patients treated with topiramate (GGT: TOP Δ=-39; PLA: Δ=-28; p=0.062); (AST: TOP Δ=-29; PLA: Δ=-22; p=0.081); (ALT: TOP Δ=-25; PLA: Δ=-21; p=0.079). Besides, a significant decrease in cholesterol levels (TOP: t=3.89; p<0.05; PLA: t=3.89; p<0.05) was reported in both groups with no difference between groups. Moreover, for biochemical analysis of glucose, low-density lipoprotein, high-density lipoprotein, non-esterified fatty acids, and triglycerides, there were no significant differences between baseline and end of treatment. Mean change in weight from baseline to the end of treatment was –0.9 kg in the TOP group, +0.3 in the PLA group.

Upon drug discontinuation, we observed no side effects.

The use of other drugs was not reported, apart from two cases of benzodiazepines intake at low doses (1 mg lorazepam; 0.5 mg alprazolam). These drugs were taken by the subjects without any medical advice, each one in just one occasion. Given the low amount the patients were not excluded from the study.

Discussion

Following alcohol detoxification, initiation of treatment aimed at relapse prevention is crucial. However, currently approved medications offer limited benefits, while other treatments are still under investigation, and they may cause problems in terms of tolerability and side effects[2]. In this multicentre, randomised, single-blind placebo-

controlled clinical trial, we intended to investigate the safety and efficacy of low dose (100 mg/day) topiramate in detoxified alcohol dependent subjects, given positive results from previous studies with higher doses, in which the burden of side effects was, however, significant[35,36]. However, in one of these studies, the burden of side effects was significant[36]. To our knowledge, this is the first placebo-controlled trial to evaluate the efficacy of low-dosage topiramate for alcohol dependence. Additionally, though data were collected in an outpatient setting, our sample was composed of heavy drinkers, with an average intake of 6 drinks per day and a history of abuse/dependence for over 3 years.

The main finding of this study is that low-dose topiramate, associated with rehabilitation, improved abstinence in the first 6 weeks after detoxification, reduced craving levels and symptoms in the areas of anxiety, depression, hostility and obsessive-compulsivity, compared to subjects receiving placebo and rehabilitation therapy.

Our results are consistent with previous placebo-controlled studies on higher doses of topiramate (both with a maximum dosage of 300 mg/day)[35,36] and with confrontation trials in which topiramate showed a good outcome compared to naltrexone[37,38]. However, in these previous studies, the optimal dose was not established. In a double-blind, randomized, placebo-controlled, 14-week clinical trial[36], six doses were adopted in the dose-escalating scheme (in mg/day): 25, 50, 100, 150, 200, and 300, with the dose of 150-300 mg/day recognized as the therapeutic dose that need to be administered to obtain a good risk-benefit profile. A major concern was related to topiramate's adverse effects. Johnson et al. [36] found that the attrition rates due to adverse events were 18.6% (34 of 183) in subjects who received topiramate. The most common adverse events were paraesthesia, anorexia, memory impairment or lack of concentration, and taste perversion. These symptoms appear

to be dose related, are prominent especially during the titration period, and usually decrease within a few days[39]. Thus, most patients, who discontinue topiramate due to its side effects, do so early in treatment, reducing potential benefits. A key objective of the present study was to establish the efficacy and side effect profile of low-dose topiramate (up to 100 mg/day), in order to improve adherence to treatment. In our sample, a low proportion of the topiramate group experienced adverse effects, but no significant difference was recorded compared to the control group. Moreover, these adverse effects were tolerable and did not cause dropouts.

Our data are consistent with a previous open-design study in which topiramate up to 75 mg/daily reduced alcohol craving and symptoms in the areas of depression and anxiety[25].

A novel finding of the present study is the influence of topiramate on hostility and obsessive-compulsivity. This is consistent with other studies in which topiramate was found to be effective in treating impulsive, aggressive and self-harmful behaviour[40], gambling[41], eating disorders[42], and obsessive-compulsive disorder[43]. Improvement in hostility and obsessive-compulsivity may contribute to the reduction of craving, relapses and withdrawal symptoms. Treatment of alcohol withdrawal and protracted withdrawal syndromes[44] is another possible mechanism involved in topiramate efficacy, given the mean improvement of withdrawal symptoms in the topiramate-treated subjects, which was significantly superior to that of the control group. This should be considered in relapse prevention strategies.

Finally, liver function tests in the treated subjects showed significantly improved results. This is obviously due to the suspension of alcohol intake, as indicated by the

decrease in GGT, but the parallel reduction in indices of hepatocellular damage point to the safety of this drug. Haematological and ECG data corroborate what has been previously described with topiramate in other psychopathological and neurological conditions[45], confirming its favourable safety profile in alcoholics.

The main limitations of our study are: 1) the small sample size; 2) the short follow-up period with lack of important information on the long-term efficacy of topiramate; 3) the single-blind design. However, it is worth highlighting that the first weeks of abstinence are crucial in the management of alcohol dependent patients, considering that craving is high, the presence of post-detoxification anhedonia is considerable[46,47], and the possibility of relapse is concrete[48].

The results of this study need to be interpreted with caution due to these limitations. Though we did not test for efficacy in different subpopulations of alcoholics, we believe that specific subpopulations of alcohol abusers, such as Cloninger type II alcoholics[49] and subjects with specific typologies of craving[50], could benefit from topiramate in terms of efficacy, given the specific pharmacodynamics properties of this drug. However, this data was not investigated by our study, and may only represent a hypothesis that need to be confirmed in future trials.

Establishing the optimal dose of topiramate has important clinical implications. It will considerably extend the population of patients receiving topiramate, it will enable those on this drug to benefit from a more tolerable adverse event profile, and it will improve compliance[51]. This approach could improve the response to topiramate in subject suffering from alcohol dependence, in parallel with the possibility to identify new pharmacogenomics variables, as recently reported by Kranzler et al.[52] for the rs2832407 C-

allele homozygotes. Future studies with larger samples, up to those tested at higher dosages, and possible comparison vs. both placebo and other dosages are mandatory.

Determining the smallest dose of topiramate resulting in efficacy, thereby achieving the optimum balance between therapeutic benefits and adverse event profile, was a notable challenge in the use of topiramate to treat alcohol dependence. The findings from our placebo-controlled study, despite the above-mentioned limitations, support the potential usefulness of topiramate, even at a dose of 100 mg/day. Topiramate could, therefore, be considered a valuable option, along with currently approved drugs, for the treatment of alcohol dependence.

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References

[1] Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. JAMA 2004; 291(10):1238-1245.

[2] Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. CNS Drugs 2004;18(8):485-504.

[3] Book SW, Myrick H (2005). Novel anticonvulsivants in the treatment of alcoholism. Expert Opin Investig Drugs 2005. 14(4):371-376.

[4] Ait-Daoud N, Malcolm RJ Jr, Johnson BA. An overview of medications for the treatment of alcohol withdrawal and alcohol dependence with an emphasis on the use of older and newer anticonvulsants. Addict Behav 2006; 31(9):1628-1649.

[5] Martinotti G, Di Nicola M, Romanelli R, et al. High and low dosage oxcarbazepine versus naltrexone for the prevention of relapse in alcohol-dependent patients. Hum Psychopharmacol 2007; 22(3):149-156.

[6] Martinotti G. Pregabalin in clinical psychiatry and addiction: pros and cons. Expert Opin Investig Drugs 2012; 21(9):1243-5.

[7] Di Nicola M, Martinotti G, Tedeschi D, et al. Pregabalin in outpatient detoxification of subjects with mild-to-moderate alcohol withdrawal syndrome. Hum Psychopharmacol 2010; 25(3):268-275.

[8] Edwards S, Kenna GA, Swift RM, et al. Current and promising pharmacotherapies, and novel research target areas in the treatment of alcohol dependence: a review. Curr Pharm Des 2011; 17(14):1323-1332.

[9] Johnson BA, Ait-Daoud N. Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. Curr Pharm Des 2010; 16(19):2103-2112.

[10] Suppes T. Review of the use of topiramate for treatment of bipolar disorders. J Clin Psychopharmacol 2002; 22(6):599-609.

[11] Harris M, Chandran S, Chakraborty N, et al. Mood-stabilizers: the archeology of the concept. Bipolar Disord 2003; 5(6):446-452.

[12] Martinotti G, Di Nicola M, Tedeschi D, et al. Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial. J Psychopharmacol 2010; 24(9):1367-1374.

[13] Kessler RC. The epidemiology of dual diagnosis. Biol Psychiatry 2004; 56(10):730-737.

[14] Czuczwar SJ, Patsalos PN. The new generation of GABA enhancers. Potential in the treatment of epilepsy. CNS Drugs 2001; 15(5):339-350.

[15] Wright SL, Banigesh A, et al. Antiischemic effects of topiramate in a transient global forebrain ischemia model: a neurochemical, histological, and behavioral evaluation. Neurochem Res 2003; 28(8):1235-1239

[16] Qian J, Noebels JL. Topiramate alters excitatory synaptic transmission in mouse hippocampus. Epilepsy Res 2003; 55(3): 225-233.

[17] Johnson BA. Uses of topiramate in the treatment of alcohol dependence. Expert Rev Neurother 2004; 4(5):751-758.

[18] Johnson BA, Swift RM, Addolorato G, et al. Safety and efficacy of GABAergic medications for treating alcoholism. Alcohol Clin Exp Res 2005; 29(2): 248-254.

[19] Miranda R Jr, MacKillop J, Monti PM, et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcohol Clin Exp Res 2008;32(3):489-497.

[20] Likhitsathian S, Saengcharnchai P, Uttawichai K, et al. Cognitive changes in topiramate-treated patients with alcoholism: a 12-week prospective study in patients recently detoxified. Psychiatry Clin Neurosci 2012;66(3):235-241.

[21] Likhitsathian S, Uttawichai K, Booncharoen H, et al. Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: a 12-week, randomized, placebo-controlled trial. Drug Alcohol Depend. 2013;133(2):440-446.

[22] Biton V, Edwards KR, Montouris GD, et al. Topiramate titration and tolerability. Ann Pharmacother 2001; 35(2):173-179.

[23] Parada M, Corral M, Mota N, et al. Executive functioning and alcohol binge drinking in university students. Addict Behav 2012; 37(2):167-172.

[24] Green A, Garrick T, Sheedy D, et al. The effect of moderate to heavy alcohol consumption on neuropsychological performance as measured by the repeatable battery for the assessment of neuropsychological status. Alcohol Clin Exp Res 2010; 34(3):443-450.

[25] Paparrigopoulos T, Tzavellas E, Karaiskos D, et al. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC Psychiatry 2011; 11:41.

[26] Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 1989; 84(11):1353-1357.

[27] Mottola CA. Measurement strategies: the visual analogue scale. Decubitus 1993; 6(5):56-58.

[28] Janiri L, Calvosa F, Dario T, et al. The Italian version of the Obsessive-CompulsiveDrinking Scale: validation, comparison with the other versions, and difference between type 1- and type 2-like alcoholics. Drug Alcohol Depend 2004; 74(2):187-195.

[29] Derogatis LR, Lipman RS, Covi L. SCL-90: An outpatient psychiatric rating scale: Preliminary report. In: Guy W, ed. ECDEU Assessment Manual for Pychopharmacology. Revised 1976. DHEW Publication No. (ADM), 1976, 76-338.

[30] Spitzer WO, Dobson AJ, Hall J, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis 1981; 34(12):585-597.

[31] Addolorato G, Abenavoli L, Leggio L, et al. How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review. Neuropsychobiology. 2005; 51(2):59-66.

[32] Addolorato G, Leggio L, Agabio R, et al. Baclofen: a new drug for the treatment of alcohol dependence. Int J Clin Pract 2006; 60(8): 1003-1008.

[33] Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992; 49(11):876-880.

[34] Gastfriend DR, Garbutt JC, Pettinati HM, et al. Reduction in heavy drinking as a treatment outcome in alcohol dependence. J Subst Abuse Treat, 2007; 33(1):71-80.

[35] Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 2003; 361:1677-1685.

[36] Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 2007; 298(14):1641-1651.

[37] Baltieri DA, Daró FR, Ribeiro PL, et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction 2008; 103(12): 2035-2044.

[38] Flórez G, Saiz PA, García-Portilla P, et al. Topiramate for the treatment of alcohol dependence: comparison with naltrexone. Eur Addict Res 2011; 17(1): 29-36.

[39] Luykx JJ, Carpay JA. Nervous system adverse responses to topiramate in the treatment of neuropsychiatric disorders. Expert Opin Drug Saf 2010; 9(4):623-631.

[40] Prado-Lima PA. Pharmacological treatment of impulsivity and aggressive behavior. Rev Bras Psiquiatr 2009; 31(2):58-65.

[41] Leung KS, Cottler LB. Treatment of pathological gambling. Curr Opin Psychiatry 2009; 22(1):69-74.

[42] McElroy SL, Guerdjikova AI, Martens B, et al. Role of antiepileptic drugs in the management of eating disorders. CNS Drugs 2009; 23(2):139-156.

[43] Berlin HA, Koran LM, Jenike MA, et al. Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry 2011; 72(5):716-721.

[44] Martinotti G, Nicola MD, Reina D, et al. Alcohol protracted withdrawal syndrome: the role of anhedonia. Subst Use Misuse 2008; 43(3-4):271-284.

[45] Kenna GA, Lomastro TL, Schiesl A, et al. Review of topiramate: an antiepileptic for the treatment of alcohol dependence. Curr Drug Abuse Rev 2009; 2(2):135-142.

[46] Hatzigiakoumis DS, Martinotti G, Giannantonio MD, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. Front Psychiatry 2011; 17(2):10.

[47] Martinotti G, Andreoli S, Reina D, et al. Acetyl-l-Carnitine in the treatment of anhedonia, melancholic and negative symptoms in alcohol dependent subjects. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35(4):953-958.

[48] Charney DA, Zikos E, Gill KJ. Early recovery from alcohol dependence: factors that promote or impede abstinence. J Subst Abuse Treat 2010; 38(1):42-50.

[49] Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50(12):975-990.

[50] Martinotti G, Di Nicola M, Tedeschi D, et al. Craving Typology Questionnaire (CTQ): a scale for alcohol craving in normal controls and alcoholics. Compr Psychiatry 2013; 54(7):925-932.

[51] Wages NA, Liu L, O'Quigley J, et al. Obtaining the optimal dose in alcohol dependence studies. Front Psychiatry 2012; 3:100.

[52] Kranzler HR, Covault J, Feinn R, et al. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry 2014;171(4):445-452.

Table 1. Socio-demographic and clinical data of subjects. Data are expressed as absolute numbers with percentage given in brackets or as mean ± standard deviation.

	Topiramate	**Control**
Sex (males)	*16 (62)*	*16 (62)*
Age	*46.6 ± 11.5*	*45.5 ± 11*
Marital status		
Single	*7 (27)*	*9 (35)*
Married	*12 (46)*	*9 (35)*
Separated/Divorced	*7 (27)*	*8 (30)*
Level of education		
Elementary School	*1 (4)*	*1 (4)*
Lower Secondary School	*7 (26)*	*6 (23)*
High School Education	*14 (55)*	*16 (62)*
Degree	*4 (15)*	*3 (11)*
Unemployment	*13*	*10*
Duration of alcohol misuse	*15.5 ± 5.2*	*17.2 ± 9.4*
Multiple substance abuse	*8 (30)*	*11 (42)*
Dual Diagnosis (Axis I)	*10 (38)*	*8 (30)*
Cloninger's Type (I)	*15*	*12*
CIWA-Ar	*6.74 ± 3.6*	*5.75 ± 4.3*
OCDS	*15.5 ± 9.2*	*12.7 ± 6.2*
VAS	*3.4 ± 3.8*	*3.9 ± 3.6*
SCL-90-R (GSI)	*0.9 ± 0.6*	*0.9 ± 0.5*

Table 2. Scores (mean ± Standard Deviation (SD)) at the Visual Analogue Scale for Craving (VAS), Obsessive Compulsive Drinking Scale (OCDS), Symptom Checklist-90-Revised (SCL-90-R), General Symptoms Index (GSI), Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) of Topiramate and Control groups at baseline (T0), and at the end of the study (T1). Level of significance are evidenced: P = Student's T test.

Measure and Treatment	**T0**		**T 1**		**P**
	Mean	**SD**	**Mean**	**SD**	
VAS					
Topiramate	*3,4*	*1,6*	*0,3*	*0,1*	*p< 0.05*
Control	*3,9*	*1,7*	*1,0*	*0,9*	*p< 0.05*
OCDS - Total					
Topiramate	*15,5*	*9.2*	*0,5*	*0.6*	*p<0.001*
Control	*12,7*	*6.2*	*5,0*	*4.6*	*p< 0.05*
SCL-90-R (GSI)					
Topiramate	*0,91*	*0.6*	*0,36*	*0.3*	*p< 0.01*
Control	*0,92*	*0.5*	*0,58*	*0.3*	*p< 0.05*
CIWA-Ar					
Topiramate	*6,7*	*3.6*	*0,5*	*0.7*	*p< 0.001*
Control	*5,7*	*4.3*	*1,1*	*2.0*	*p< 0.05*

Fig. 1. Diagram of subject flow by treatment group

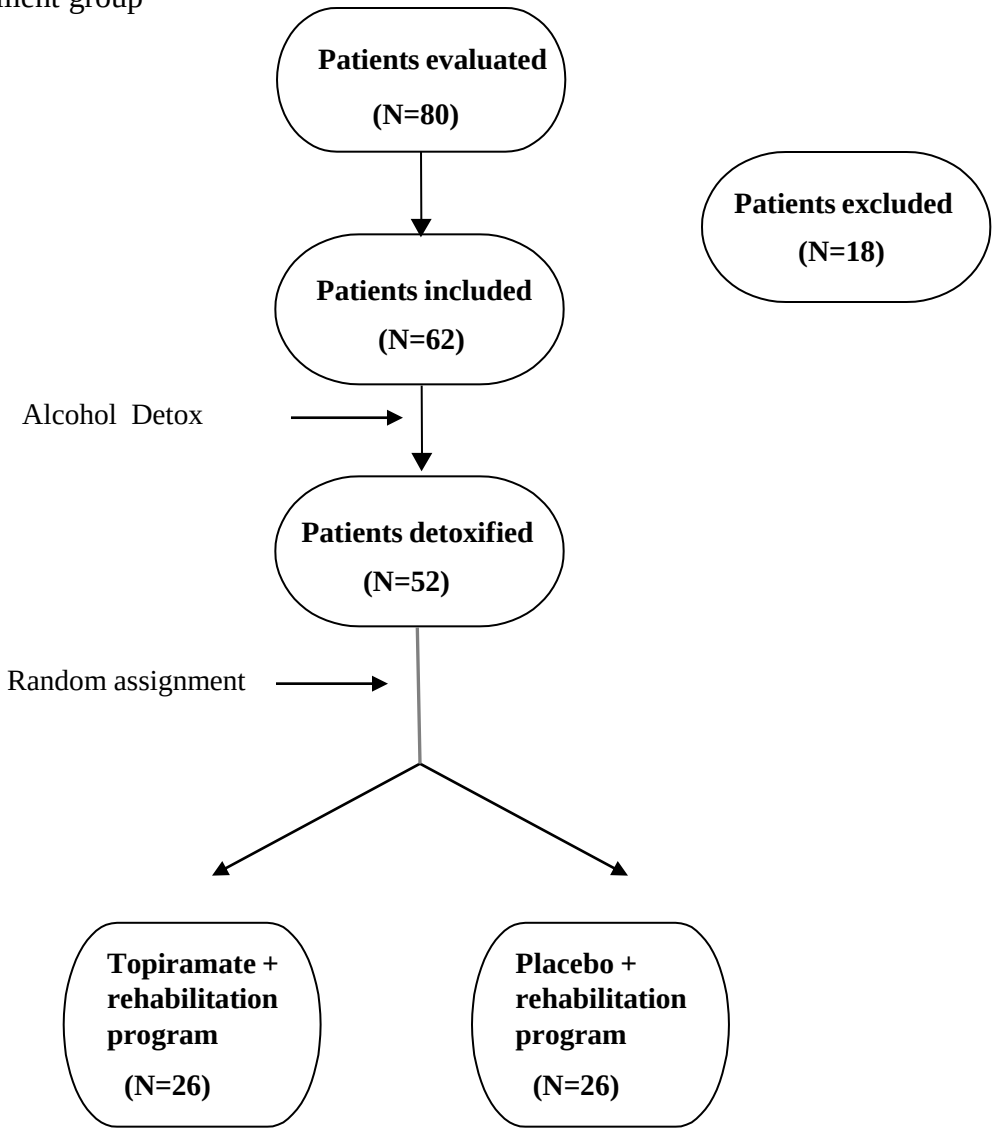
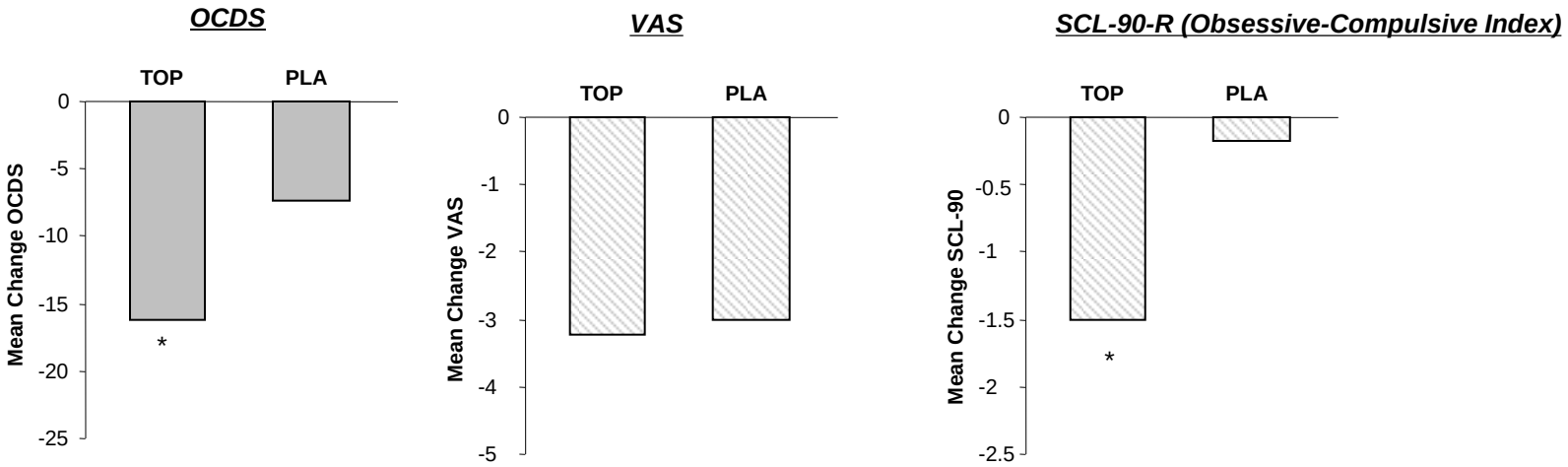


Fig 2: Obsessive Compulsive Drinking Scale (OCDS), Visual Analogue Scale for Craving (VAS), and Obsessive-compulsive subscale of the Symptom Check List (SCL-90-R) mean change from baseline at the last assessment (T1)
* = p<.01



Dear Editor,

These (in bold) are the answers to the points proposed by the reviewer. As supplemental data file I have also attached a further revised version with the revised points in yellow.

Reviewer #1:

The issue of using low doses of topiramate is critical, hence studies like this one are welcome and interesting. Results are relevant and the manuscript is well-written. I only have a few minor comments:

The sentence "To our knowledge, this is the first placebo-controlled trial to evaluate the efficacy of topiramate for alcohol dependence." should be revised to specify that it refers to low doses, i.e., 100mg/d.

As suggested the sentence has been revised.

Introduction and Discussion should be revised taking into account a recent RCT with topiramate 200mg/d (Kranzler et al. Am J Psychiatry 2014). In particular, the Discussion should emphasize the importance of future studies testing the pharmacogenetics of topiramate 100mg/d.

The recent RCT and the importance of future studies has been emphasized.

Reviewer #2:

The utility of topiramate for the treatment of alcohol and other drug use disorders is limited by significant dose-dependent side effects and clinical trials showing the efficacy of low dose topiramate are potentially of great interest. This paper reports on a randomized single blind investigation of the efficacy of topiramate up to 100 mg bid in reducing alcohol use and craving following detoxification. The background is detailed, statistical analysis is appropriate, and methods and results are clearly explained.

Below are observations/suggestions:

1) 'Abstinence was confirmed by performing blood alcohol tests at each outpatient follow-up visit' (methods p 8) It would be helpful to report the number of visits and blood/toxicology drug tests.

As suggested we reported in the text the number of visits and tests

2) 'Subjects were strongly advised against using drugs that could potentially

influence craving for alcohol' (methods p 8). Please report any other drug use in the results.

In the results we have now reported the use of other drugs.

3) Results: Please report n,% and/or t values for all comparisons.

As suggested we reported T values for all comparisons and specified numbers where more significant

4) Results: Were blood alcohol tests confirming self-reported use?

Yes, blood alcohol tests confirmed the use reported by the patients. We have now declared in the study that bac confirmed what was reported by the patients.

5) '18 were then excluded (as they did not fulfil inclusion criteria)..' (results p 10) were there any common exclusion factors? They could be summarized in the consort graph.

We reported the reasons for exclusion in the results section.

6) 'Ten patients were excluded during the detoxification phase' (results p 10) please report the reason for exclusion.

We have now reported the reasons for exclusion in the results section.

7) '6 of treatment' (results p11) should read '6 weeks of treatment'.

The correction has been addressed.

8) The one described in the manuscript is a small to medium treatment effect. In the opinion of the Authors future studies should be comparing low dose topiramate with placebo or with higher dose topiramate? And what should the appropriate sample size be?

We think that other studies with low-dosage of topiramate should be replicated with a sample size of 100 to 250 subjects, as for the placebo-controlled study with higher dosages of topiramate. A comparison trial could also be of some interest. We have now added these considerations in the discussion section.

Reviewer #3:

This manuscript describes a single-blind, placebo-controlled trial of topiramate 100

mg/day in 52 alcohol-dependent patients. The findings show that low-dose topiramate can be efficacious in reducing drinking measures in alcoholics, which is an important contribution to the literature.

The major concern I have is over the analytic approach. In a number of cases (e.g., GGT, AST, ALT concentrations), the analysis compares pre- and post-treatment values, rather than comparing topiramate and placebo groups, which can be misleading. A preferable analytic approach would be to use a two-factor analysis in which both time (pre/post) and medication group (topiramate/placebo) are analyzed as main effects and the interaction of these factors is also examined.

We agree with the reviewer We have performed a comparison between topiramate and placebo, comparing the differences (delta) between baseline and the end of the treatment for both the treatment. A significant difference was not evidence, but only a trend. We reported this data in the results. Probably, the low sample size, the relatively good percentage of responders in the placebo group, and the short timeframe of the study are factors that can explain this data.

In addition, there are a number of omissions or errors that should be addressed.

1. There is no mention of the approval of nalmefene (Selincro) in the EU (p. 2).

We have now reported this data, that was not available when the first draft of this paper was prepared.

2. There is an older study (http://www.ncbi.nlm.nih.gov/pubmed/18215213) and three recent studies of topiramate that should be cited:
http://www.ncbi.nlm.nih.gov/pubmed/22443246,
http://www.ncbi.nlm.nih.gov/pubmed/23906999, and
http://www.ncbi.nlm.nih.gov/pubmed/24525690.

As suggested these studies have been reported.

3. Although patients were recruited from both inpatient and outpatient sources, I could not find the proportion of patients from each of those sources and whether there were differences in the proportion of each in the two treatment groups. The inclusion of this measure in Table 1 would be helpful to the reader.

All the patients recruited were in an outpatients setting. The Day-Hospital of Psychiatry and Drug Dependence may be defined as an outpatients unit, where the subjects remain the time required for the pharmacological and/or psychosocial therapy. The Day-Hospital is opened only in the morning, and it does not allow clients to stay during the night as in a inpatient unit. We have now specified this aspect in the methods.

4. The logistic regression analysis of abstinence, in which the OCDS was a

significant predictor, doesn't take into account the fact that the drinking measures in the OCDS may have been confounded with the outcome measure.

Also excluding the items correlated with the use of alcohol the differences remained significant. We data had been already reported in the result section: "Abstinent patients in both study groups showed significantly lower OCDS scores than relapsed patients, even after the exclusion of alcohol consumption items (P<0.01)"

5. Although statistical significance is reported for a variety of analyses throughout the manuscript, the statistics themselves (e.g., chi-square values, regression beta statistics) are omitted, with only p-values being provided. In some cases, statements are made concerning significant differences and the actual values (e.g., GGT, AST, ALT concentrations) are not provided. Similarly, the overall study completion rates in the two medication groups are not provided.

As suggested we have now reported these important details.

6. There is no information concerning the single-blind study design. Presumably, the investigators knew which patients received active or placebo medication. If that's true, it should be made clear whether those individuals interacted with the patients, which could confound the results. If available, it would also be useful to know which treatment the patients believed they received. In any case, this should be included as a limitation on p. 15.

In agreement with the reviewer we have now included this as a limitation. However, we report that the psychometric evaluations have been made by blind raters and the investigators did not influenced the evaluation.

7. On p. 13, there are statements made regarding prior topiramate studies (references 32 and 33) that are incorrect. Although in the multi-center topiramate study (ref. 33) there was greater dropout due to topiramate adverse events, this was not true in the single-site study (ref. 32), where the active medication was very well tolerated. Similarly, the same two citations are used in relation to dosing of 150-300 mg/day. This is incorrect because both studies used a maximal dosage of 300 mg/day.

As suggested, this issue has been addressed in the discussion section.

8. The statement on p. 13 is incorrect: "To our knowledge, this is the first placebo-controlled trial to evaluate the efficacy of topiramate for alcohol dependence."

In agreement with the reviewer we have now corrected the statement.

9. There are typographical, spelling, or grammatical errors throughout the manuscript (e.g., "die" instead of "day" when describing daily dosages).

We have now adequately revised the paper.

10. In the penultimate paragraph on p. 15, what the authors believe should not be included, except as a hypothesis, as there is nothing in the current study that addresses whether subpopulations of alcoholics would specifically benefit from topiramate treatment.

In this study the analysis of subpopulations receiving topiramate has not been made. However, to do and propose hypothesis could be of some interest, indicating possible new therapautical strategies. However, we have modified and clarified the sentence.

Supplemental Data File (.doc, .tif, pdf, etc.)

Click here to download Supplemental Data File (.doc, .tif, pdf, etc.): yellow revised version Topiramate 25-may-2014.doc

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