Abstract: 299 words
Text: 3,059 words
Tables: 3
Figures: 3

Effects of Topiramate Therapy on Serum Bicarbonate Concentration in a Sample of 10,279 Veterans

Michelle S. Naps, M.D.,[1,2*] Shirley H. Leong, Ph.D.,[1*] Emily E. Hartwell, Ph.D.,[1,3] Christopher T. Rentsch, Ph.D.[4,5,6] and Henry R. Kranzler, M.D.,[1,3]

[1]Mental Illness Research, Education and Clinical Center, Crescenz Veterans Affairs Medical Center, Philadelphia, PA 19104
[2]School of Engineering and Applied Sciences, University of Pennsylvania, Philadelphia, PA 19104
[3]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104
[4]VA Connecticut Healthcare System, US Department of Veterans Affairs, West Haven, CT
[5]Department of Internal Medicine, Yale School of Medicine, New Haven, CT
[6]Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

Corresponding Author:
Henry R. Kranzler, M.D.
Center for Studies of Addiction
University of Pennsylvania Perelman School of Medicine
3535 Market Street, Suite 500
Philadelphia, PA 19104
Email: kranzler@pennmedicine.upenn.edu
Telephone: 215-746-1943

*These authors contributed equally to this work.

Disclosure: Dr. Kranzler is a member of advisory boards for Dicerna Pharmaceuticals, Sophrosyne Pharmaceuticals, and Enthion Pharmaceuticals; a consultant to Sobrera Pharmaceuticals; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last three years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, Otsuka, and Pear Therapeutics; and a holder of U.S. patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued 26 January 2021. The other authors have no disclosures to make.

Abstract

Background: Topiramate, which is increasingly being used to treat alcohol use disorder (AUD), is commonly associated with reduced serum bicarbonate concentrations. However, estimates of the prevalence and magnitude of this effect are from small samples and do not address whether topiramate's effects on acid-base balance differ in the presence of an AUD or by topiramate dosage.

Methods: Veterans Health Administration electronic health record (EHR) data was used to identify patients with a minimum of 180 days of topiramate prescription for any indication and a propensity score matched control group. We differentiated patients into two subgroups based on the presence of a diagnosis of AUD in the EHR. Baseline alcohol consumption was determined using Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) scores in the EHR. Analysis also included a three-level measure representing mean daily dosage. The topiramate-associated changes in serum bicarbonate concentration were estimated in difference-in-differences linear regression models. A serum bicarbonate concentration <17 mEq/L was considered to represent possible clinically significant metabolic acidosis.

Results: The cohort comprised 4,287 topiramate-treated patients and 5,992 propensity score matched controls with a mean follow-up period of 417 days. The mean topiramate-associated reductions in mean serum bicarbonate concentration were <2 mEq/L in the low (<= 88.75), medium (>88.75 and <=141.70), and high (> 141.70) mg/d dosage tertiles, irrespective of AUD history. Concentrations <17 mEq/L occurred in 1.1% of topiramate-treated patients and 0.3% of controls and were not associated with alcohol consumption or an AUD diagnosis.

Conclusions: The excess prevalence of metabolic acidosis associated with topiramate treatment does not differ with dosage, alcohol consumption, or the presence of an AUD. Baseline and periodic serum bicarbonate concentration measurements are recommended during topiramate therapy. Patients prescribed topiramate should be educated about the

symptoms of metabolic acidosis and urged to report their occurrence promptly to a healthcare provider.

Key Words: Topiramate, Metabolic Acidosis, Bicarbonate, Alcohol Treatment, Adverse Event

Introduction

Topiramate, a sulfamate-substituted monosaccharide that is structurally related to fructose, has multiple neurotransmitter- and enzyme-mediated effects. It was originally approved in 1996 by the Food and Drug Administration for the treatment of epilepsy.[1] In 2004, the drug was approved for the prophylaxis of migraine headache[2] and in 2012, it was approved in combination with phentermine for weight loss.[3] Across these multiple indications, from 2014-2019, there were over 8 million topiramate prescriptions filled annually in the United States.[4]

Efforts to expand topiramate's clinical utility have included studies in a range of psychiatric disorders, including bipolar disorder and substance use disorders. Although its off-label use to treat psychiatric disorders is controversial[5-8], topiramate is considered an evidence-based treatment for moderate-to-severe alcohol use disorder (AUD).[9-11]

Topiramate blocks voltage-activated sodium and calcium channels, potentiates GABA activity at non-benzodiazepine $GABA_A$ receptors, and attenuates glutamate activity at AMPA/kainate receptors.[12,13] In renal tissue, topiramate inhibits carbonic anhydrase (CA) II, IV, and XII, three CA isoforms that promote bicarbonate reabsorption in the proximal tubule and hydrogen excretion in the distal tubule.[14] As a result, some topiramate-treated patients develop a mixed renal tubular acidosis with hyperchloremia.[15,16]

Case reports of topiramate-induced acid-base disturbance first emerged in 1999,[17,18] and topiramate prescribing information was revised in 2003 to include severe metabolic acidosis as a potential rare adverse event.[19] More frequently, topiramate use leads to mild decrements in serum bicarbonate levels that are of unclear clinical significance. A retrospective cohort study of 54 topiramate-treated patients in an outpatient neurology clinic showed a mean maximal reduction in serum bicarbonate concentration of 5.1 mEq/L (95% CI 3.7 to 6.5) during treatment.[20] In a retrospective case series study of 350 veterans, those prescribed topiramate had a statistically significant decrease of 2.7 mEq/L in serum bicarbonate concentration during the first year of therapy, with one patient having a bicarbonate concentration of <17 mEq/L

without clinical effects.[21] The mean (standard deviation [SD]) serum bicarbonate nadir concentration during treatment in this series was 25.3 (3.1) mEq/L.

Although topiramate is widely prescribed and commonly associated with reduced bicarbonate levels, the extent to which its effects on acid-base balance are clinically relevant is unclear, particularly at higher dosages or in susceptible subgroups. The recommended daily dosage of topiramate for treating epilepsy is 200-400 mg, 100 mg for migraine prophylaxis, and 46 mg (combined with 7.5 mg/day of phentermine) for weight loss.[16,22] As a treatment for AUD, topiramate has been studied at a dosage of 75-300 mg/day.[12,23-25] Several small studies in adults showed no significant correlation of topiramate dosage with serum bicarbonate level.[21,26,27] Jovanovic et al[26] reported an inverse relationship between topiramate treatment duration and serum bicarbonate concentration, with frequent occurrence of low serum bicarbonate concentration during treatment extending beyond 5 years. However, another study showed no association between treatment duration and serum bicarbonate concentration.[27]

Topiramate's effects on acid-base balance could compound those associated with AUD. In acute care settings, severe alcohol intoxication and alcohol withdrawal states are associated with respiratory acidosis, alcoholic ketoacidosis, dehydration, and electrolyte disturbances.[32-34] Furthermore, alcohol-related liver disease, an entity that encompasses the damage states of fatty liver, hepatitis, and cirrhosis, can increase the risk of metabolic acidosis.[35] Also, protein-calorie malnutrition and deficiencies of micronutrients (e.g., folate, thiamine, and magnesium) are more common in patients with severe AUD[36-39] and can adversely affect acid-base balance[40-42], as can the metabolic effects of alcohol on cellular redox potential.[43-45]

Johnson et al[23] reported that among 371 subjects with alcohol dependence randomized to receive topiramate or placebo, the mean plasma bicarbonate concentration was lower for the topiramate-treated group than the control group at the end of treatment (mean difference: 2.50 mEq/L [95% CI, 1.89-3.11 mEq/L), with no effect on plasma pH and no cases of metabolic acidosis that required medical intervention. These results are consistent with multiple other

clinical trials of topiramate for treating AUD,[24,28-31] in which there were no serious adverse events related to metabolic acidosis.

Given the range of topiramate dosages across therapeutic indications and the potential for metabolic derangements associated with heavy alcohol consumption to exacerbate the metabolic acidosis induced by topiramate, we compared the effects of topiramate on serum bicarbonate concentration at different dosage levels and in patients differentiated by the presence of an AUD diagnosis. To conduct the study analyses, we used electronic health record (EHR) data from the largest integrated healthcare system in the United States.

Materials and Methods

Study Population

We accessed EHR data, including patient demographics, diagnoses, laboratory test results, and pharmacy dispensing records from the Department of Veterans Affairs (VA) Corporate Data Warehouse through the VA Informatics and Computing Infrastructure.[46] For this analysis, we included patients who had received a topiramate prescription that was filled at an outpatient Veterans Health Administration (VHA) pharmacy and propensity score matched controls with no history of topiramate treatment. We identified all patients who received topiramate for at least 180 days, with coverage of at least 144 of those days and no gap longer than 30 days, for any indication between January 1, 2009 and October 1, 2015. We limited patients to those attending the VHA clinics that most frequently generated topiramate prescriptions, including primary care, neurology, psychiatry, women's health, substance use disorder treatment, pain medicine, endocrinology, and physical medicine and rehabilitation. Potential controls included all patients who attended one of the relevant clinics on a randomly selected date in each calendar year but never received topiramate. We chose index dates that enabled us to follow topiramate-treated patients and controls over similar calendar time. The index date was defined as the first fill date for topiramate-treated patients and the random clinic visit date for controls. We used a 12-month washout period to identify new episodes of

topiramate treatment. Therefore, patients who received topiramate at any point were eligible for inclusion only after a one-year period without topiramate treatment.

Propensity Score Matching

To reduce the risk of confounding by indication, we generated propensity scores, which were used to adjust for the conditional probability of being prescribed topiramate given a set of covariates associated with the receipt of topiramate.[47] Propensity score matching balances the treatment and control groups on factors potentially involved in treatment selection, similar to treatment allocation in a randomized controlled trial.[48] Propensity scores were estimated separately for patients with and without a history of AUD.

Variables used in the propensity score multivariable logistic regression models (Supplemental Table S1) were selected *a priori* based on clinical knowledge[49] and included age, race, smoking status, body mass index (BMI), hospitalization frequency during the year prior to the index date, history of various medical and mental health conditions, and history of various substance use disorders. To address historical trends in topiramate use, we included the index year and a site prescribing pattern variable, defined as the proportion of patients who initiated topiramate stratified by site and year. We also included variables that captured attendance at various medical, surgical, and mental health clinics and the total number of clinic visits prior to the index date. Lastly, variables denoting outpatient treatment with opioid, muscle relaxant, anti-depressant, and nonsteroidal anti-inflammatory medications were included in the model. All main effect variables were tested for two-way interaction, and significant two-way interaction terms ($p<.05$) were included in the final propensity score model. The model C-statistic was 0.846 for patients with a history of AUD and 0.886 for patients with no history AUD, indicating adequate discrimination in both models.[50]

After propensity score generation, we conducted the propensity score matching within pre-specified subgroups of patients based on index year and baseline scores on the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) measure.[51] Each exposed patient

was matched to up to five unexposed patients with index dates in the same calendar year, using a greedy matching algorithm.[52] After propensity score matching, patients without pre-treatment and post-treatment serum bicarbonate results were excluded from the cohort. Also, currently prescribed medications associated with metabolic acidosis[53-54] were exclusionary (Supplemental Table S2). Finally, we aggregated the strata to create the full matched cohort.[55]

Measures and Follow-up

We differentiated patients with a history of AUD from those without such a history based on the occurrence at any time prior to baseline of one inpatient or two outpatient codes for alcohol dependence (303.x) or alcohol abuse (305.00-305.03) using the *International Classification of Disease, Ninth revision, Clinical Modification*. A current AUD status was given when the history of AUD was within one year prior to the index date. Baseline alcohol consumption was determined using the most recent AUDIT-C score recorded in the EHR during the year prior to the index date. The AUDIT-C is a three-item questionnaire used to detect hazardous drinking and screen for alcohol use disorders by querying the quantity and frequency of alcohol consumption.[50] Systematic annual screening with the AUDIT-C has been implemented within VHA outpatient clinics since 2004.[56]

We determined serum bicarbonate concentrations using uncorrected venous serum total carbon dioxide (tCO_2) concentrations. As bicarbonate comprises approximately 95% of tCO_2 and there is no direct laboratory method for measuring bicarbonate concentration, the serum bicarbonate concentrations reported in this study are tCO_2 concentration results from lab auto-analyzers.[57] The pretreatment serum bicarbonate concentration was defined as the most recent measurement within the year prior to the index date. The post-treatment serum bicarbonate concentration was defined as the average of all serum bicarbonate measurements between 30 days after the index date and 7 days after the end of topiramate treatment. The minimum serum bicarbonate concentration during this post-treatment period was used to identify patients with a threshold of <17 mEq/L to define a markedly low concentration.[16]

We followed all patients from their index date for a maximum of two years or until their last VHA visit or death. Additionally, topiramate-treated patients were censored at 30 days after the end of their last topiramate prescription. To ensure equal follow-up time within matched sets, controls were censored at the total follow-up time of their matched topiramate-treated patient.

Statistical Analyses

All statistical analyses were performed separately for patients with and without a history of AUD. We used multivariable difference-in-difference (DiD) linear regression models[58-59] to estimate the differential change in serum bicarbonate concentrations from pretreatment to post-treatment between the topiramate-treated and control groups. We performed subgroup analyses by average daily topiramate dosage during follow-up. The topiramate dosages were categorized into low, medium, and high tertiles (<= 88.75, >88.75 and <=141.70, and > 141.70 mg/d, respectively). As there may have been residual confounding not addressed by propensity score matching, models were adjusted for age, the total number of non-topiramate prescriptions during follow-up, and any characteristic that differed between the treatment and control groups. Differing characteristics were identified based on a phi coefficient > 0.05 for categorical variables and SMD > 0.1 for continuous variables.

Finally, we compared the odds of markedly low serum bicarbonate concentration between the topiramate-treated and control groups using χ-square analysis. We applied the Breslow-Day test for homogeneity to determine whether the odds ratios differed based on a history of AUD prior to the index date or baseline AUDIT-C category.

All statistical analyses were performed using SAS Enterprise Guide version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

As shown in in Supplemental Figure 1, the initial sample comprised 1,044,029 patients, including 38,366 topiramate-treated patients and 1,005,663 potential controls. Propensity score matching yielded 22,332 patients with a history of AUD and 77,478 patients without a history of AUD. The application of exclusion criteria (i.e., absence of a baseline or follow-up bicarbonate concentration result, receipt of an exclusionary medication, or control matched to an excluded topiratment-treated patient) led to the exclusion of 19,951 patients with a history of AUD and 69,580 patients without a history of AUD. The propensity score matched cohort characteristics were similar before and after exclusions, except for a lower mean number of past-year dermatology clinic visits in the cohort after exclusions (SMD=0.57) among patients without a history of AUD (Supplemental Table S3). The treatment and control groups in the propensity score matched cohort were well balanced (SMD < 0.10), except for a higher number of past-year neurology clinic visits in the treatment groups (history of AUD: SMD=0.12 pre-exclusions vs. 0.16 post-exclusions; no history of AUD: SMD=0.14 pre-exclusions vs. 0.12 post-exclusions) (Supplemental Tables S4 and S5).

The final matched sample was predominantly male (74.8%), with a mean (SD) age of 49.2 (13.4) years, and 23.2% had a history of an AUD diagnosis, of whom 57.4% had a current AUD diagnosis (Table 1). Among individuals without a history of AUD a larger proportion of men than women received topiramate treatment (p=0.02). However, the phi coefficient for sex did not meet the threshold for inclusion as a characteristic that differed between the topiramate-treated and control groups (phi=0.02). Topiramate-treated patients had a significantly lower mean baseline [SD] serum bicarbonate concentration than controls (26.49 [2.96] vs. 27.19 [2.81] mEq/L; p<.001). On subgroup analysis, this difference was present irrespective of AUD history, AUDIT-C score, or topiramate dosage subgroups (Table 2).

(Tables 1 and 2 Here)

Figure 1 shows the mean absolute changes in serum bicarbonate concentrations among topiramate-treated patients and controls by AUD history. Among topiramate-treated patients, the mean (SD) serum bicarbonate concentration decreased from 26.61 (3.07) mEq/L to 24.73 (2.79) mEq/L among those with a history of AUD and from 26.45 (2.94) to 24.89 (2.74) mEq/L among those with no history of AUD. Among controls, the mean (SD) serum bicarbonate concentration decreased from 27.02 (2.91) to 26.83 (2.62) mEq/L among those with a history of AUD and from 27.25 (2.78) to 27.14 (2.53) mEq/L among those with no history of AUD. In the DiD analyses, topiramate treatment was associated with a reduction in mean serum bicarbonate concentration of 1.69 mEq/L (95% CI,1.46-1.91) among patients with a history of AUD and 1.45 mEq/L (95% CI, 1.33-1.56) among those with no history of AUD.

Topiramate-treated patients received a mean (SD) topiramate dosage of 129 (87) mg/d for a mean (SD) duration of 417 (189) days. Figures 2 and 3 show the mean absolute changes in serum bicarbonate concentrations among topiramate-treated patients and controls by topiramate mean daily dosage level. Among patients with a history of AUD, the topiramate-associated reduction in serum bicarbonate concentration was 1.03 mEq/L (CI, 0.60-1.46) at a low dosage, 1.92 mEq/L (CI, 1.54-2.30) at a medium dosage, and 1.96 mEq/L (CI, 1.60-2.32) at a high dosage (Table 3). Among patients without a history of AUD, the reduction was 1.14 mEq/L (CI, 0.93-1.35) at a low dosage,1.64 mEq/L (CI, 1.44-1.84) at a medium dosage, and 1.55 mEq/L (CI, 1.34-1.75) at a high dosage (Table 3).

(Figures 1-3 and Table 3 Here)

Serum bicarbonate concentration decreased to less than 17 mEq/L during the follow-up period in 1.1% of topiramate-treated patients and 0.32% of control patients (OR=3.56, 95%CI, 2.09-6.06; *P*<.001). We found no association of AUD history or baseline AUDIT-C score category with the occurrence of a markedly low bicarbonate concentration.

Discussion

The study results substantiate the low-grade reductions in serum bicarbonate concentration that are frequently seen in patients on topiramate therapy and the potential for sporadic cases of severe metabolic acidosis. There were no clinically significant differences in topiramate-associated serum bicarbonate concentration changes as a function of an AUD diagnosis. These results are particularly important because AUD is highly prevalent in the United States, with a 12-month prevalence of 13.9% and a lifetime prevalence of 29.1% among adults.[60] AUD commonly co-occurs among individuals with epilepsy[61-62], an indication for topiramate treatment. Moreover, topiramate is increasingly used off-label and recommended as a first-line pharmacotherapy for AUD without comorbid seizure or migraine disorders.[63]

The topiramate-associated serum bicarbonate concentration changes were calculated using the mean serum bicarbonate concentration for each patient during a specified period after topiramate initiation. As expected, we found a less pronounced effect on serum bicarbonate concentration than previous studies that reported maximal reductions during topiramate treatment. In all subgroups included in the DiD analyses, the mean post-exposure bicarbonate concentrations were well above the lower limit of the reference range for serum bicarbonate concentration. Nevertheless, even low-grade metabolic acidosis can have deleterious health consequences, including osteopenia[64-65], sarcopenia[66], and progression of chronic kidney disease[67].

Pretreatment and periodic serum bicarbonate concentration measurements are recommended during topiramate therapy.[16] Patients prescribed topiramate should be educated about the symptoms of metabolic acidosis and urged to report their occurrence promptly to a healthcare provider. Topiramate treatment for longer than 12 months has been associated with osteopenia[68]. Clinicians should consider individualized strategies to prevent and detect bone loss in patients on long-term treatment with topiramate, as with other antiepileptic medications that reduce bone density.[69] Also, a reassessment of topiramate dosage and treatment duration

may be indicated for patients who experience changes in health status or medication regimen that could increase the risk of metabolic acidosis.

Limitations

The use of retrospective EHR data presents several limitations. Although propensity score matching is used in non-experimental settings to reduce sample selection bias, it does not preclude the existence of unrecognized confounders as is also the case with randomization in a prospective clinical trial. In this study, there was a particularly high proportion of exclusions in the sample after propensity score matching. Nonetheless, the balance achieved by propensity score matching was retained after the additional exclusions.

The serum bicarbonate concentrations were measured on an outpatient basis as part of metabolic test panels ordered during diverse clinical contexts, such as routine interval, urgent care, and emergency department visits. Therefore, there may have been unrecognized differences between the treatment and control groups related to the medical status of the patients when the laboratory specimens were obtained. Additionally, the bicarbonate concentration measurements during the follow-up period did not occur at prespecified time points. Further, the study data did not include blood gas panel results, which would have provided information about the extent to which cases of metabolic acidosis were associated with respiratory compensation. Finally, although the inclusion of data on adherence to dosage would augment the findings reported here, unfortunately, information on adherence was not available in our data, as is the case in many health data systems.

Contribution

This is the largest systematic assessment of the effects of topiramate treatment on serum bicarbonate concentrations and the first to investigate whether AUD, alcohol consumption levels, and topiramate dosage are risk factors for topiramate-induced metabolic acidosis. The study provides useful information to topiramate prescribers regarding the low likelihood that the medication will cause severe metabolic acidosis, either in patients with AUD

or those without such a diagnosis, expanding the normative data available for serum bicarbonate concentrations among topiramate-treated patients.

References

1. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed May 31, 2022.
2. Nadin C. Topiramate: the evidence for its therapeutic value in the prevention of migraine. *Core Evidence*. 2005;1(2):103-124.
3. Alfaris N, Minnick AM, Hopkins CM, Berkowitz RI, Wadden TA. Combination phentermine and topiramate extended release in the management of obesity. *Expert Opin Pharmacother*. 2015;16(8):1263-1274. doi:10.1517/14656566.2015.1041505
4. Kane SP. Topiramate, ClinCalc DrugStats Database, Version 2021.10. http://clincalc.com/DrugStats/Drugs/Topiramate. Updated September 12, 2021. Accessed June 4, 2022.
5. Nourredine M, Jurek L, Angerville B, et al. Use of Topiramate in the Spectrum of Addictive and Eating Disorders: A Systematic Review Comparing Treatment Schemes, Efficacy, and Safety Features. *CNS Drugs*. 2021;35(2):177-213. doi:10.1007/s40263-020-00780-y
6. Pigott K, Galizia I, Vasudev K, Watson S, Geddes J, Young AH. Topiramate for acute affective episodes in bipolar disorder in adults. *Cochrane Database Syst Rev.* 2016; (9):CD003384. doi:10.1002/14651858.CD003384.pub3.
7. Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav*. 2011;21(1):1-11. doi:10.1016/j.yebeh.2011.03.011
8. Kmietowicz Z. Company pays over $81m for allegedly promoting topiramate for unapproved uses. *BMJ*. 2010;340:c2848. doi:10.1136/bmj.c2848.
9. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings: A Systematic Review and Meta-analysis. *JAMA*. 2014;311(18):1889–1900. doi:10.1001/jama.2014.3628

10. Blodgett JC, Del Re AC, Maisel NC, Finney JW. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcohol Clin Exp Res.* 2014;38(6):1481-1488.

11. US Veterans Health Administration/Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.* Washington, DC: Veterans Health Administration; 2015 revision.

12. Guglielmo, R., Martinotti, G., Quatrale, M., Ioime, L., Kadilli, I., Di Nicola, M., & Janiri, L. (2015). Topiramate in Alcohol Use Disorders: Review and Update. *CNS Drugs*, 29, 383-395. doi:10.1007/s40263-015-0244-0

13. White H. S. (2005). Molecular pharmacology of topiramate: managing seizures and preventing migraine. *Headache,* 45, S48-56. doi:10.1111/j.1526-4610.2005.4501006.x

14. Mirza N, Marson AG, Pirmohamed M. Effect of topiramate on acid–base balance: extent, mechanism and effects. *Br J Clin Pharmacol*. 2009;68(5):655-661. doi:10.1111/j.1365-2125.2009.03521.x

15. Philippi H, Boor R, Reitter B. Topiramate and metabolic acidosis in infants and toddlers. *Epilepsia*. 2002;43:744–747

16. Topamax (topiramate) [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc; 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020844s041lbl.pdf. Accessed May 31, 2022.

17. Wilner A, Raymond K, Pollard R: Topiramate and metabolic acidosis. *Epilepsia.* 1999;40(6):792–5. doi:10.1111/j.1528-1157.1999.tb00781.x

18. Stowe CD, Bollinger T, James LP, et al. Acute mental status changes and hyperchloremic metabolic acidosis with long-term topiramate therapy. *Pharmacotherapy.* 2000;20(1):105–9. doi:10.1592/phco.20.1.105.34662.

19. US Food and Drug Administration. *MedWatch Medical Product Safety Information.* December 2003. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/UCM189811.zip Archived at https://archive.org/web. Accessed June 4, 2022.

20. Garris SS, Oles KS. Impact of topiramate on serum bicarbonate concentrations in adults. Ann Pharmacother 2005; 39: 424– 426.

21. Sciegienka A, Argo T, Cantrell M, Alexander B. Association between topiramate use and serum bicarbonate levels in a veteran population. *Ann Pharmacother*. 2015;49(6):670-3. doi:10.1177/1060028015579197.

22. Qsymia (phentermine and topiramate extended-release) [package insert]. Winchester, KY: VIVUS Inc; 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022580s000lbl.pdf. Accessed May 31, 2022.

23. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA*. 2007;298(14):1641-1651. doi:10.1001/jama.298.14.1641

24. Martinotti G, Di Nicola M, De Vita O, Hatzigiakoumis DS, Guglielmo R, Santucci B, Aliotta F, Romanelli R, Verrastro V, Petruccelli F, Di Giannantonio M, Janiri L. Low-Dose Topiramate in Alcohol Dependence, Journal of Clinical Psychopharmacology: 2014;34(6):709-715. doi:10.1097/JCP.0000000000000228

25. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. 2018;320(8):815-824. doi:10.1001/jama.2018.11406

26. Jovanović M, Sokić D, Grabnar I, et al. Effect of Long-term Topiramate Therapy on Serum Bicarbonate and Potassium Levels in Adult Epileptic Patients. Annals of Pharmacotherapy. 2014;48(8):992-997. doi:10.1177/1060028014534397

27. Mirza NS, Alfirevic A, Jorgensen A, Marson AG, Pirmohamed M. Metabolic acidosis with topiramate and zonisamide: an assessment of its severity and predictors. *Pharmacogenet Genomics*. 2011;21(5):297-302. doi:10.1097/FPC.0b013e3283441b95

28. Batki SL, Pennington DL, Lasher B, et al. Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. *Alcohol Clin Exp Res*. 2014;38(8):2169-2177. doi:10.1111/acer.12496

29. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*. 2003;361(9370):1677-1685. doi:10.1016/S0140-6736(03)13370-3

30. Kranzler HR, Covault J, Feinn R, et al. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism [published correction appears in Am J Psychiatry. 2014 May 1;171(5):585]. *Am J Psychiatry*. 2014;171(4):445-452. doi:10.1176/appi.ajp.2013.13081014

31. Kranzler HR, Morris PE, Pond T, et al. Prospective randomized pharmacogenetic study of topiramate for treating alcohol use disorder. *Neuropsychopharmacology*. 2021;46(8):1407-1413. doi:10.1038/s41386-020-00945-9

32. Langhan ML. Acute alcohol intoxication in adolescents: frequency of respiratory depression. *J Emerg Med*. 2013;44(6):1063-1069. doi:10.1016/j.jemermed.2012.11.041

33. Allison MG, McCurdy MT. Alcoholic metabolic emergencies. *Emerg Med Clin North Am*. 2014;32(2):293-301. doi:10.1016/j.emc.2013.12.002

34. Flannery AH, Adkins DA, Cook AM. Unpeeling the Evidence for the Banana Bag: Evidence-Based Recommendations for the Management of Alcohol-Associated Vitamin and Electrolyte Deficiencies in the ICU. *Crit Care Med*. 2016;44(8):1545-1552. doi:10.1097/CCM.0000000000001659

35. Scheiner B, Lindner G, Reiberger T, et al. Acid-base disorders in liver disease. *J Hepatol*. 2017;67(5):1062-1073. doi:10.1016/j.jhep.2017.06.023

36. Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. *Alcohol Clin Exp Res*. 1995;19(3):635-641. doi:10.1111/j.1530-0277.1995.tb01560.x

37. Lieber CS. Relationships between nutrition, alcohol use, and liver disease. Alcohol Res Health. 2003;27(3):220-31.

38. Palmer BF, Clegg DJ. Electrolyte Disturbances in Patients with Chronic Alcohol-Use Disorder. *N Engl J Med*. 2017;377(14):1368-1377. doi:10.1056/NEJMra1704724

39. Baj J, Flieger W, Teresiński G, Buszewicz G, Sitarz E, Forma A, Karakuła K, Maciejewski R. Magnesium, Calcium, Potassium, Sodium, Phosphorus, Selenium, Zinc, and Chromium Levels in Alcohol Use Disorder: A Review. J Clin Med. 2020;9(6):1901. doi:10.3390/jcm9061901

40. Moskowitz A, Lee J, Donnino MW, Mark R, Celi LA, Danziger J. The Association Between Admission Magnesium Concentrations and Lactic Acidosis in Critical Illness. *J Intensive Care Med*. 2016;31(3):187-192. doi:10.1177/0885066614530659

41. Zheng Y, Cantley LC. Toward a better understanding of folate metabolism in health and disease. *J Exp Med*. 2019;216(2):253-266. doi:10.1084/jem.20181965

42. Attaluri P, Castillo A, Edriss H, Nugent K. Thiamine Deficiency: An Important Consideration in Critically Ill Patients. *Am J Med Sci*. 2018;356(4):382-390. doi:10.1016/j.amjms.2018.06.015

43. Grasselli E, Compalati AD, Voci A, et al. Altered oxidative stress/antioxidant status in blood of alcoholic subjects is associated with alcoholic liver disease. *Drug Alcohol Depend*. 2014;143:112-119. doi:10.1016/j.drugalcdep.2014.07.013

44. Comporti M, Signorini C, Leoncini S, et al. Ethanol-induced oxidative stress: basic knowledge. *Genes Nutr*. 2010;5(2):101-109. doi:10.1007/s12263-009-0159-9

45. Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health. 2003;27(4):277-84.

46. U.S. Department of Veterans Affairs. VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457. Available at: https://www.research.va.gov/programs/vinci/default.cfm. Accessed June 4, 2022.

47. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.

48. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Stat Med*. 2007;26(1):20-36. doi:10.1002/sim.2739

49. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. 2002;155(2):176-184. doi:10.1093/aje/155.2.176

50. Hosmer D, Lemeshow S. Applied Logistic Regression, New York, John Wiley and Sons, 2000.

51. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998;158(16):1789-95.

52. Parsons, LS. Performing a 1: N case-control match on propensity score. Proceedings of the 29th Annual SAS Users Group International Conference, SAS Institute; 2004; Montreal, Canada.

53. Liamis G, Milionis HJ, Elisaf M. Pharmacologically-induced metabolic acidosis: a review. *Drug Saf*. 2010;33(5):371-391. doi:10.2165/11533790-000000000-00000

54. Pham AQ, Xu LH, Moe OW. Drug-Induced Metabolic Acidosis. *F1000Res*. 2015;4:F1000 Faculty Rev-1460. Published 2015 Dec 16. doi:10.12688/f1000research.7006.1

55. Wang SV, Jin Y, Fireman B, et al. Relative Performance of Propensity Score Matching Strategies for Subgroup Analyses. *Am J Epidemiol*. 2018;187(8):1799-1807. doi:10.1093/aje/kwy049

56. Bradley KA, Williams EC, Achtmeyer CE, Volpp B, Collins BJ, Kivlahan DR. Implementation of evidence-based alcohol screening in the Veterans Health Administration. *Am J Manag Care*. 2006;12(10):597-606.

57. Bihari S, Galluccio S, Prakash S. Electrolyte measurement - myths and misunderstandings-Part II. *J Crit Care*. 2020;60:341-343. doi:10.1016/j.jcrc.2020.06.004

58. Donald SG, Lang K 2007 Inference with difference-in-differences and other panel data. Review of Economics and Statistics, 89, 221–233.

59. Lechner M. The estimation of causal effects by difference-in-difference methods. Foundations and Trends in Econometrics. 2011;4:165–224.

60. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS. Epidemiology of DSM-5 Alcohol Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015 Aug;72(8):757-66. doi: 10.1001/jamapsychiatry.2015.0584.

61. Bakken IJ, Revdal E, Nesvåg R, Brenner E, Knudsen GP, Surén P, Ghaderi S, Gunnes N, Magnus P, Reichborn-Kjennerud T, Camilla Stoltenberg, Trogstad LI, Håberg SE, Brodtkorb E. Substance use disorders and psychotic disorders in epilepsy: a population-based registry study. Epilepsy Res. 2014 Oct;108(8):1435-43. doi: 10.1016/j.eplepsyres.2014.06.021

62. Selassie AW, Wilson DA, Martz GU, Smith GG, Wagner JL, Wannamaker BB. Epilepsy beyond seizure: a population-based study of comorbidities. *Epilepsy Res*. 2014;108(2):305-315. doi:10.1016/j.eplepsyres.2013.12.002

63. Del Re AC, Gordon AJ, Lembke A, Harris AH. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. Addict Sci Clin Pract. 2013;8(1):12.

64. Mitch WE. Metabolic and clinical consequences of metabolic acidosis. *J Nephrol*. 2006;19 Suppl 9:S70-S75.

65. Raphael KL. Metabolic Acidosis and Subclinical Metabolic Acidosis in CKD. *J Am Soc Nephrol*. 2018;29(2):376-382. doi:10.1681/ASN.2017040422

66. Kraut JA, Madias NE. Adverse Effects of the Metabolic Acidosis of Chronic Kidney Disease. *Adv Chronic Kidney Dis*. 2017;24(5):289-297. doi:10.1053/j.ackd.2017.06.005

67. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int*. 2011;79(3):356-362. doi:10.1038/ki.2010.388

68. Ali II, Herial NA, Orris M, Horrigan T, Tietjen GE. Migraine prophylaxis with topiramate and bone health in women. *Headache*. 2011;51(4):613-616. doi:10.1111/j.1526-4610.2011.01863.x

69. Dussault PM, Lazzari AA. Epilepsy and osteoporosis risk. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(6):395-401. doi:10.1097/MED.0000000000000366

Figure Legends

Figure 1. Serum Bicarbonate Concentration in Patients by Baseline Alcohol Use Disorder Status

Figure 2. Serum Bicarbonate Concentration in Patients with a History of Alcohol Use Disorder by Topiramate Dosage

Figure 3. Serum Bicarbonate Concentration in Patients with no History of Alcohol Use Disorder by Topiramate Dosage

Table 1. Baseline Patient Demographic and Clinical Characteristics[a,b]

	History of AUD			No History of AUD		
	Topiramate (n=988)	Control (n=1393)	*P* Value	Topiramate (n=3299)	Control (n=4599)	*P* Value
Age, mean (SD), y	50.2 (11.4)	49.5 (12.0)	.15	49.4 (13.4)	48.7 (14.2)	.04
Sex						
Female	153 (15.5)	194 (13.9)	.29	894 (27.1)	1354 (29.4)	.02
Male	835 (84.5)	1199 (86.1)		2405 (72.9)	3245 (70.6)	
Race						
White	775 (78.4)	1083 (77.8)	.62	2642 (80.1)	3728 (81.1)	.13
Black or African American	189 (19.1)	272 (19.5)		559 (16.9)	704 (15.3)	
American Indian/Alaskan Native	7 (0.7)	8 (0.6)		28 (0.9)	50 (1.1)	
Asian	2 (0.2)	6 (0.4)		13 (0.4)	34 (0.7)	
Native Hawaiian or Other Pacific Islander	5 (0.5)	14 (1.0)		24 (0.7)	37 (0.8)	
Mixed	10 (1.0)	10 (0.7)		33 (1.0)	46 (1.0)	
Pretreatment HCO_3, mean (SD)	26.61 (3.07)	27.02 (2.91)	<.001	26.45 (2.93)	27.25 (2.78)	<.001
Pretreatment AUDIT-C score, mean (SD)	2.9 (3.8)	3.0 (3.9)	.59	1.0 (1.7)	1.1 (1.7)	.04
BMI, mean (SD)	29.7 (6.0)	29.4 (5.9)	.15	31.1 (6.3)	30.7 (6.4)	.005
No. of medical diagnoses, mean (SD)[c]	0.9 (1.1)	0.9 (1.0)	.76	0.8 (1.1)	0.8 (1.0)	.35
No. of psychiatric diagnoses, mean (SD)[d]	2.0 (1.1)	2.0 (1.0)	.39	1.2 (1.1)	1.2 (1.1)	.72
No. of substance abuse diagnoses, mean (SD)[e]	0.5 (0.6)	0.5 (0.6)	.90	0.3 (0.5)	0.3 (0.5)	.95
Current smoker (past year)	699 (70.8)	965 (69.3)	.44	1365 (41.4)	1887 (41.0)	.76
Opioid pharmacotherapy[f]	282 (28.5)	410 (29.4)	.64	819 (24.8)	1201 (26.1)	.20

Abbreviations: AUD, alcohol use disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HCO_3, serum bicarbonate concentration.

a. Data are reported as a number (percentage) of patients unless otherwise specified.
b. Propensity score matched patients in final analytic sample.
c. Medical diagnoses (i.e., pain, cardiovascular, and other) are listed in Table S3 in the Supplement.
d. Psychiatric diagnoses are listed in Table S3 in the Supplement.
e. Substance abuse diagnoses are listed in Table S3 in the Supplement.
f. Prescribed opioid medication dispensed as an outpatient.

Table 2. Baseline Serum Bicarbonate Concentration by Clinical Subgroup

Clinical Subgroup	Topiramate (n=4287)		Control (n=5992)		
	No. (%)	Serum HCO3 (SD), mEq/L	No. (%)	Serum HCO3 (SD), mEq/L	*P* Value
History of AUD	988 (23.0)	26.61 (3.07)	1393 (23.2)	27.02 (2.91)	<.001
Current AUD diagnosis	588 (13.7)	26.63 (3.10)	778 (13.0)	26.90 (2.87)	.10
Past AUD diagnosis	400 (9.3)	26.60 (3.04)	615 (10.3)	27.18 (2.95)	.002
AUDIT-C score					
0	447 (10.4)	26.68 (3.11)	608 (10.1)	26.98 (2.99)	.12
1-3	225 (5.2)	26.80 (2.99)	337 (5.6)	27.11 (2.78)	.20
4-7	156 (3.6)	26.46 (3.04)	211 (3.5)	26.92 (2.96)	.15
8+	160 (3.7)	26.30 (3.13)	237 (4.0)	27.10 (2.83)	.008
Topiramate dosage					
Low (<=88.75 mg/d)	278 (6.5)	26.74 (2.81)	371 (6.2)	27.27 (2.83)	.02
Medium (>88.75 & <=141.70 mg/d)	332 (7.7)	27.00 (3.05)	486 (8.1)	27.02 (2.99)	.94
High (>141.70 mg/d)	378 (8.8)	26.17 (3.22)	536 (8.9)	26.86 (2.87)	<.001
No history of AUD	3299 (77.0)	26.45 (2.93)	4599 (76.8)	27.25 (2.78)	<.001
AUDIT-C score					
0	1762 (41.1)	26.53 (3.06)	2320 (38.7)	27.29 (2.92)	<.001
1-3	1278 (29.8)	26.38 (2.80)	1909 (31.9)	27.21 (2.62)	<.001
4+	259 (6.0)	26.24 (2.71)	370 (6.2)	27.20 (2.71)	<.001
Topiramate dosage					
Low (<=88.75 mg/d)	1072 (25.0)	26.59 (2.78)	1452 (24.2)	27.21 (2.81)	<.001
Medium (>88.75 & <=141.70 mg/d)	1122 (26.2)	26.65 (2.92)	1652 (27.6)	27.19 (2.82)	<.001
High (>141.7 mg/d)	1105 (25.8)	26.11 (3.07)	1495 (24.9)	27.35 (2.71)	<.001

Abbreviations: AUD, alcohol use disorder; HCO_3, serum bicarbonate concentration.
SI conversion factor: bicarbonate, 1:1 conversion to millimoles per liter.

Table 3. Difference-in-Difference Estimates of Serum Bicarbonate Concentration Changes by AUD History and Topiramate Dosage[a]

	History of AUD		No History of AUD	
Topiramate Dosage[b]	**Estimate (95% CI)**[c]	***P* Value**	**Estimate (95% CI)**[c]	***P* Value**
Low (<=88.75 mg/d)				
Δ HCO_3 (Topiramate)	-1.45 (-1.77 to -1.13)	<.001	-1.24 (-1.40 to -1.08)	<.001
Δ HCO_3 (Control)	-0.42 (-0.70 to -0.14)	.003	-0.10 (-0.23 to 0.04)	.15
Difference-in-differences	-1.03 (-1.46 to -0.60)	<.001	-1.14 (-1.35 to -0.93)	<.001
Medium (>88.75 & <=141.70 mg/d)				
Δ HCO_3 (Topiramate)	-2.12 (-2.42 to -1.83)	<.001	-1.75 (-1.90 to -1.59)	<.001
Δ HCO_3 (Control)	-0.21 (-0.45 to -0.04)	.10	-0.10 (-0.23 to 0.02)	.11
Difference-in-differences	-1.92 (-2.30 to -1.54)	<.001	-1.64 (-1.84 to -1.44)	<.001
High dosage (>141.70 mg/d)				
Δ HCO_3 (Topiramate)	-2.00 (-2.27 to -1.72)	<.001	-1.67 (-1.83 to -1.52)	<.001
Δ HCO_3 (Control)	-0.03 (-0.27 to 0.20)	.77	-0.13 (-0.26 to 0.00)	.06
Difference-in-differences	-1.96 (-2.32 to -1.60)	<.001	-1.55 (-1.75 to -1.34)	<.001

Abbreviations: AUD, alcohol use disorder; HCO_3, serum bicarbonate concentration.
SI conversion factor: bicarbonate, 1:1 conversion to millimoles per liter
a. Unadjusted and adjusted models did not differ for any of the estimates.
b. Average daily dosages were calculated from pharmacy fill records.
c. Unit of measure for the serum bicarbonate concentration estimates is mEq/L.