Balancing Risk and Benefit in Heavy Drinkers Treated With Topiramate:
Implications for Personalized Care

Richard Feinn, PhD[a]; Brenda Curtis, PhD[b]; and Henry R. Kranzler, MD[b,c,*]

ABSTRACT

Background: Despite topiramate's ability to reduce heavy drinking, its adverse effects may limit its clinical utility.

Method: To evaluate the risks and benefits of topiramate, we reanalyzed data from a completed trial of the medication in 138 heavy drinkers whose goal was to reduce their drinking to safe levels. We used the number of patients who had no heavy drinking days during the last 4 weeks of treatment to calculate topiramate's number needed to treat (NNT). To balance the risks and benefits of topiramate, we adjusted the NNT using 2 different levels of adverse event severity: moderate or greater (NNT-AE_{mod+}) and severe or greater (NNT-AE_{sev+}). This measure helps to guide the clinical use of topiramate in heavy drinkers by incorporating both its beneficial and adverse effects in a single measure. Because a polymorphism (rs2832407) in the gene encoding a kainate receptor subunit appears to moderate topiramate's effects in heavy drinkers, we repeated the analyses based on rs2832407 genotype (C-homozygote vs A-allele carrier) in the European American subsample (n = 122).

Results: Overall, the NNT for topiramate was 5.29, the NNT-AE_{mod+} was 7.52, and the NNT-AE_{sev+} was 6.12. Among European Americans with the rs2832407*CC genotype, the NNT was 2.28, the NNT-AE_{mod+} was 2.63, and the NNT-AE_{sev+} was 2.56. In contrast, for rs2832407*A-allele carriers, the NNT was 180.00, the NNT-AE_{mod+} was 322.16, and the NNT-AE_{sev+} was 217.45.

Conclusions: In this sample of heavy drinkers, topiramate had a clinically important treatment effect that was most evident in European Americans with the rs2832407*CC genotype. In that group, in particular, it had a robust treatment effect, even when adjusted for adverse events.

Trial Registration: ClinicalTrials.gov identifier: NCT00626925

J Clin Psychiatry 2016;77(3):e278–e282
dx.doi.org/10.4088/JCP.15m10053

[a]Department of Medical Sciences, Frank Netter School of Medicine, Quinnipiac University, Hamden, Connecticut
[b]Center for Studies of Addiction, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia
[c]VISN 4 Mental Illness Research, Education and Clinical Center, Philadelphia VAMC, Pennsylvania
**Corresponding author:* Henry R. Kranzler, MD, Treatment Research Center, University of Pennsylvania Perelman School of Medicine, 3900 Chestnut St, Philadelphia, PA 19104 (kranzler@mail.med.upenn.edu).

Topiramate has been shown to reduce consumption of a variety of substances of abuse. It has been most widely studied in alcohol treatment, and it reduces drinking in alcohol-dependent individuals and heavy drinkers.[1–4] A meta-analysis showed that topiramate's efficacy in alcohol treatment is substantially greater than that of naltrexone or acamprosate,[5] medications that are approved by the US Food and Drug Administration and most commonly prescribed for alcohol treatment. Consistent with its robust therapeutic effect, the rate of topiramate prescription for alcohol treatment in the US Veterans Health Administration more than doubled from 2009 to 2012.[6] Topiramate also increases the likelihood of cigarette abstinence among smokers.[7,8] Some studies have also shown an effect of topiramate on abstinence from cocaine,[9,10] though a recent study[11] found no such effect.

In addition to its efficacy, tolerability is important in a clinician's choice of a medication to treat an alcohol use disorder (AUD) and a patient's decision to take the medication. Based on topiramate's actions in multiple neurotransmitter and enzyme systems,[12,13] it has a variety of adverse effects, the most common of which are somnolence, fatigue, weight loss, and nervousness.[14] Less common adverse effects of topiramate include cognitive difficulties (eg, confusion, psychomotor slowing; decreased concentration, attention, and memory; speech or language problems), renal calculi, metabolic acidosis, and visual disturbances (including, rarely, secondary glaucoma).

In a study[4] of 138 heavy drinkers whose goal was to reduce their drinking to safe levels, we found that topiramate reduced heavy drinking days (HDDs) and increased abstinent days significantly more than placebo. Further, in the subsample of European Americans (n = 122), the effect was moderated by rs2832407, a single nucleotide polymorphism (SNP) in *GRIK1*, the gene that encodes the GluK1 subunit of the kainate receptor. Thus, the use of topiramate to treat heavy drinking may be most appropriate in individuals with a specific rs2832407 genotype (the frequency of which varies widely by population).

Although the only serious adverse event seen in our study was in the placebo group, patients receiving topiramate reported significantly more adverse events overall (mean = 5.5 [SD = 3.1]) than placebo patients (mean = 3.0 [SD = 2.5]) ($P < .001$) and events of at least moderate severity (mean = 1.8 [SD = 1.3]) than placebo patients (mean = 0.4 [SD = 0.7]) ($P < .001$). Topiramate patients reported a significantly greater likelihood of numbness/tingling, change in taste, loss of appetite, weight loss, difficulty concentrating, and difficulty with memory.[4]

Despite the clinical relevance of the risk-benefit relationship, there are no published measures that jointly reflect the therapeutic and adverse effects of topiramate in treating AUD. Here, we calculated number needed to treat (NNT) and adjusted it for reported adverse

Clinical Points

- Heavy drinking is prevalent in the population and commonly associated with a variety of adverse medical and social effects. There are comparatively few treatments with more than modest efficacy to reduce heavy drinking. Topiramate was effective in reducing heavy drinking among individuals with alcohol dependence, especially those homozygous for the *GRIK1* rs2832407*C allele.
- Because topiramate has a variety of pharmacologic effects, it is associated with adverse effects that limit its clinical use. A risk-benefit analysis that used no heavy drinking as a criterion for treatment success and adjusted for adverse events showed that topiramate compared favorably to other currently used alcohol treatment medications, with the greatest benefit seen among rs2832407*C-allele homozygotes.

events, using data from our topiramate trial.[4] The NNT is the estimated number of patients who must receive an intervention to achieve a successful outcome in 1 patient, relative to the effects of placebo treatment. We adjusted the NNT for 2 levels of adverse events: those of a moderate or greater severity (which may be most relevant to a patient's choice whether to undergo treatment) and, separately, those that received a severe or greater rating (which may be most relevant for a prescriber's choice as to whether to prescribe the treatment). Finally, we repeated all of the comparisons separately by rs2832407 genotype (C-allele homozygotes vs A-allele carriers).

We hypothesized that the adverse event–adjusted NNT for topiramate would be substantially lower than the NNTs reported in the literature for either naltrexone or acamprosate.[5] Further, on the basis of a prior finding that the rs2832407 genotype in *GRIK1* moderated the response to topiramate,[4] we hypothesized that European American individuals with the rs2832407*CC genotype would have an adverse event–adjusted NNT that is lower than that of A-allele carriers, reflecting greater efficacy of the medication in the CC-genotype group. Further, on the basis of a report by Ray et al,[15] in which rs2832407*C homozygotes showed a lower risk of adverse events than A-allele carriers, we expected that the impact of adjusting NNT for adverse events would be more modest in the CC genotype patients.

METHOD

Overview

We reanalyzed data from a 12-week, double-blind, randomized, placebo-controlled trial[4] of topiramate in a sample of 138 heavy drinkers. In that study, 67 patients (48.6%) were randomly assigned to receive topiramate and 71 patients (51.4%) received placebo. Most patients were male (placebo: n = 41 [58%], topiramate: n = 45 [67%]) and European American (placebo: n = 66 [93%], topiramate: n = 56 [84%]). The genotype distribution among European Americans was as follows: 21 topiramate-treated patients were rs2832407*C homozygotes and 35 were A-allele carriers (ie, either heterozygotes or A-allele homozygotes) and the comparable numbers in the placebo group were 30 and 36, respectively. Additional information on the study sample is provided in Kranzler et al.[4] The original study was registered on ClinicalTrials.gov (identifier: NCT00626925).

Patients were seen weekly for the first 6 weeks to allow a gradual increase in topiramate dosage from 25 mg/d to a maximum of 200 mg/d (or a comparable number of matching placebo capsules). They were seen once every 2 weeks for the remaining 6 weeks. The Timeline Followback[16] was administered to cover the 90-day pretreatment period, and it was repeated at each treatment visit to estimate the number of HDDs since the last visit (ie, 4 or more drinks in a day for women and 5 or more drinks in a day for men). At each visit, patients were also queried regarding the treatment-emergent occurrence of 19 adverse events that have been associated with topiramate treatment. For each adverse event endorsed, patients were asked about the nature of the adverse event and the level of functional impairment associated with it, which was categorized as mild (no impairment), moderate (some change in activities), severe (substantial limitations), life threatening/disabling, or fatal, resulting in a 5-point rating scale. Reported adverse events were followed until they resolved. Additional information on the study methods is provided in Kranzler et al.[4]

Analyses

Number needed to treat is the number of patients that needed topiramate treatment (compared with placebo) to prevent 1 patient from having an HDD during the last 4 weeks (ie, weeks 9–12) of treatment. In this calculation, patients who withdrew prior to week 12 (15% overall) were coded as not successfully treated. When evaluating the NNT, the lower the value, the larger the treatment effect.

We calculated the proportion of patients in each treatment group that reported at least 1 adverse event and the average severity rating of reported events (absent = 0, mild = 1, moderate = 2, severe = 3, and life threatening/disabling = 4). We adjusted the NNT separately using 2 levels of adverse event severity: at least 1 adverse event rated as moderate or greater in severity and at least 1 adverse event rated as severe or greater. These categories were chosen, despite being overlapping, to address patient concerns (ie, adverse events of moderate or greater severity), which are more likely to center on comfort and safety, and prescriber concerns (ie, adverse events that are severe or greater), which are more likely to center on safety as counterweights to efficacy.

The NNT was calculated by taking the inverse of the absolute risk reduction, the difference in event rates between the topiramate and placebo groups during the 12 weeks of treatment. We calculated 95% confidence limits (CLs) for NNT using the method of Wilson.[17] We adjusted the NNT by the severity of reported adverse events.[18] We also performed a subgroup analysis by genotype (CC vs A-allele carrier) within European Americans (n = 122) to evaluate the impact on clinical utility of the moderator effect of rs2832407. Although values of NNT are often rounded up to the nearest whole number to provide a readily interpretable estimate,[19]

Table 1. Rate of Heavy Drinking, Adverse Events, Number Needed to Treat, and Adverse Event–Adjusted Number Needed to Treat by Treatment Group and Genotype Group

			European-American Subsample (n = 122)			
	Full Sample (n = 138)		rs2832407* C-Allele Homozygotes, n = 51 (41.8%)		rs2832407* A-Allele Carriers, n = 71 (58.2%)	
Measure	Placebo, n = 71 (51.4%)	Topiramate, n = 67 (48.6%)	Placebo, n = 30 (58.8%)	Topiramate, n = 21 (41.2%)	Placebo, n = 36 (50.7%)	Topiramate, n = 35 (49.3%)
No heavy drinking days, %	17	36	13	57	19	20
Adverse event rated as moderate or greater in severity, %	48	78	53	67	44	89
Adverse event rated as severe or greater, %	3	16	3	14	3	20
NNT (95% CL)	5.29 (3.05, 23.67)		2.28 (1.57, 5.71)		180.00 (5.22, –5.57)	
NNT-AE_{mod+}	7.52		2.63		322.16	
NNT-AE_{sev+}	6.12		2.56		217.45	

Abbreviations: CL = confidence limits, NNT = number needed to treat, NNT-AE_{mod+} = NNT adjusted for moderate or greater adverse events, NNT-AE_{sev+} = NNT adjusted for severe or greater adverse events.

we present the values carried out to 2 decimal places to allow comparisons with adverse event–adjusted NNTs and with NNTs from comprehensive reviews of naltrexone[20] and acamprosate.[21]

RESULTS

Full Sample (n = 138)

Efficacy. Table 1 shows the proportion of patients experiencing no HDDs during the last month of treatment. As reported in Kranzler et al[4] in the full sample, 36% of patients treated with topiramate reported no HDDs during the last month of treatment compared to 17% in the placebo group, an NNT of 5.29.

Adverse events. The vast majority of patients reported at least 1 adverse event, including 96% of the topiramate group and 86% of the placebo group, a nonsignificant difference ($\chi^2_1 = 3.73$, $P = .053$). Although most adverse events were rated as mild, the mean severity rating was significantly greater in the topiramate group (1.3 [SD = 0.4]) than in the placebo group (1.1 [SD = 0.5]) ($F_{1,136} = 8.86$, $P = .003$). Among topiramate patients, 78% reported at least 1 adverse event of moderate or greater severity compared to 48% for placebo. Taking into account the presence of moderate or greater adverse events yielded an adverse event–adjusted NNT (NNT-AE_{mod+}) of 7.52. The percentage of patients reporting a severe or greater adverse event was 16% for topiramate and 3% for placebo, yielding an adverse event–adjusted NNT (NNT-AE_{sev+}) of 6.12.

European American Subgroup (n = 122)

The last 2 columns of Table 1 show the response and adverse event rates for European American patients by treatment and genotype group.

Efficacy. As previously reported,[4] rs2832407 moderated the effect of topiramate in European Americans. Among rs2832407*C homozygotes, 57% of those treated with topiramate had no HDDs during the last month of treatment, compared to 13% of placebo patients, an NNT of 2.28. In contrast, among A-allele carriers, there was a very small difference in the likelihood of no HDDs during the last month of treatment (20% of topiramate patients and 19% of placebo patients), an NNT of 180.00. The 95% CL for this NNT (5.22, –5.57) shows that the conditions were equivalent, ie, topiramate had no discernible effect on the risk of HDDs in the last month of treatment.

Adverse events. Nearly all individuals (ie, 92%) in both rs2832407 genotype groups experienced 1 or more adverse events ($\chi^2_1 = 0.02$, $P = .90$). Among rs2832407*C homozygotes, topiramate-treated patients reported a mean adverse event severity of 1.3 (SD = 0.3), compared with 1.1 (SD = 0.5) in the placebo group, a nonsignificant difference ($F_{1,49} = 3.31$, $P = .075$). Among A-allele carriers treated with topiramate, the mean adverse event severity was 1.5 (SD = 0.3), compared with 1.1 (SD = 0.6) in the placebo group, a highly significant difference ($F_{1,69} = 11.51$, $P = .001$). The interaction of medication group × genotype group on this severity measure was not significant ($F_{1,118} = 0.83$, $P = .37$).

A majority of rs2832407*C homozygotes reported an adverse event that was moderate or greater in severity, including 67% of topiramate patients and 53% of placebo patients, a nonsignificant difference ($\chi^2_1 = 0.91$, $P = .34$). The NNT-AE_{mod+} was 2.63 (ie, when adjusted for adverse events that were moderate or greater in severity). Fourteen percent of topiramate patients and 3% of placebo patients experienced a severe adverse event, yielding an NNT-AE_{sev+} of 2.56.

Among rs2832407*A-allele carriers, 89% of topiramate patients and 44% of placebo patients experienced a moderate or greater adverse event. This yielded an NNT-AE_{mod+} of 322.16. Twenty percent of topiramate patients and 3% of placebo patients experienced a severe adverse event, an NNT-AE_{sev+} of 217.45.

Accounting for the rate of treatment completion did not change the results substantially (data not shown), a finding consistent with the high rate of completion in both medication groups (topiramate: 82.1%; placebo: 87.3%).

DISCUSSION

Topiramate, although more efficacious in treating alcohol dependence than either naltrexone or acamprosate,[5] produces a number of adverse effects that can limit its use. We found that a SNP (rs2832407) in *GRIK1* moderated topiramate's effect in reducing HDDs,[4] identifying a highly responsive subgroup of heavy drinkers among European Americans. To capture both the beneficial and adverse effects of topiramate from that study, we calculated the NNT to reduce heavy drinking and adjusted it using 2 levels of adverse event severity. Overall, we found that the NNT for topiramate was 5.29, a robust treatment effect when compared with the unadjusted NNTs that have been reported for both naltrexone in preventing a relapse to heavy drinking (NNT = 9.09)[20] and acamprosate in reducing the risk of returning to any drinking after detoxification (NNT = 9.09).[21] The NNT for topiramate, when adjusted for adverse effects of the medication, was 7.52 (when considering moderate or greater adverse events) or 6.12 (when considering only severe adverse events). Thus, as hypothesized, even after we adjusted for adverse events, topiramate yielded a more robust alcohol treatment effect than either naltrexone or acamprosate. Reducing the risk of HDDs is clinically important, as serious medical and psychiatric adverse outcomes[22] and elevated mortality risk[23] are associated with this pattern of drinking. Thus, the use of topiramate to treat heavy drinking appears to be clinically useful. These estimates also compare favorably with the effects of medications that are efficacious in the treatment of major depression, including both tricyclic antidepressants, which, unadjusted for adverse events, had a median NNT of 9, and selective serotonin reuptake inhibitors, which, unadjusted, had a median NNT of 7.[24]

We found that topiramate had a much more robust effect in promoting no HDDs in individuals with the rs2832407*CC genotype. In this group, the NNT was 2.28 unadjusted and about 2.6 adjusted for either of the 2 severity levels of adverse effects. In striking contrast, among patients with an rs2832407*A allele, the NNT adjusted for moderate or severe adverse effects was 322.16 and for severe adverse effects was 217.45. These findings argue strongly against the use of topiramate to treat heavy drinking in patients with the rs2832407*A allele, as the benefit relative to placebo is extremely small, particularly when accounting for the adverse effects of the medication.

The finding that the impact of adjusting for adverse effects was much smaller among European Americans with the rs2832407*CC genotype than those with 1 or 2 A alleles at this locus is consistent with the findings reported by Ray et al.[15] They found a greater mean level of adverse effects among topiramate-treated patients who were rs2832407*A-allele carriers than those who were homozygous for the C allele. However, we did not find an effect of genotype on the mean severity of topiramate-induced adverse effects. Thus, although topiramate's efficacy in reducing heavy drinking is greater in patients with the rs2832407*CC genotype than in A-allele carriers, the question of whether the CC-genotype group also tolerates the medication better than do A-allele carriers remains to be answered.

Although we adjusted the NNT to account for adverse effects, we did not ascertain the relative importance of the beneficial and adverse effects of the medication to the patients participating in the study. This can be partially overcome by having the patients rate the utility value of each outcome,[25] which could then be incorporated in the risk-benefit analysis. Moreover, the severity rating may not fully capture the clinical impact of different adverse events. For example, despite a similar rating, paresthesia and visual changes may be of different importance to the patient. Another study limitation is that the sample was not very large (n = 138), particularly in the subgroup analyses (CC genotype, n = 56; A-allele carriers, n = 66).

The findings reported here have a number of clinical implications. First, the NNT for topiramate (5.29) compares favorably to that of antidepressants for the treatment of depression (median = 7–9) and is superior to that of the 2 medications approved to treat alcohol dependence: naltrexone and acamprosate (9.09 for both, though it should be noted that the criteria on which these NNTs are based differ across the 3 medications, limiting direct comparisons among them). Adjusting for adverse events does not substantially alter those findings. However, the NNT for topiramate in rs2832407*C homozygotes (2.28) was substantially lower than that for the overall sample or for A-allele carriers (180.00), suggesting that topiramate should be prescribed only to individuals with the CC genotype, though efforts to replicate the findings are needed. Ultimately, the clinical utility of this approach will depend on the widespread availability of SNP genotyping for use in clinical decision making.

Submitted: April 15, 2015; accepted June 29, 2015.
Online first: February 16, 2016.
Drug names: acamprosate (Campral and others), naltrexone (ReVia and others), topiramate (Topamax and others).
Potential conflicts of interest: **Dr Kranzler** has been a consultant or advisory board member for Alkermes, Indivior, Lilly, Lundbeck, and Otsuka; and is also a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which is supported by AbbVie, Ethypharm, Lilly, Lundbeck, and Pfizer. **Drs Feinn** and **Curtis** have no disclosures.
Funding/support: Supported by National Institutes of Health grants P60 AA03510 and K24 AA13736 to Dr Kranzler from the National Institute on Alcohol Abuse and Alcoholism and the VISN 4 Mental Illness Research, Education, and Clinical Center of the US Department of Veterans Affairs.
Role of the sponsor: The funding agencies played no role in the conduct of the study or in the preparation of the manuscript.

REFERENCES

1. 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.
2. Johnson BA, Rosenthal N, Capece JA, et al; Topiramate for Alcoholism Study Group. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA*. 2007;298(14):1641–1651.
3. 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.
4. 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.
5. Blodgett JC, Del Re AC, Maisel NC, et al. A meta-analysis of topiramate's effects for

individuals with alcohol use disorders. *Alcohol Clin Exp Res*. 2014;38(6):1481–1488.
6. Del Re AC, Gordon AJ, Lembke A, et al. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. *Addict Sci Clin Pract*. 2013;8(1):12.
7. Anthenelli RM, Blom TJ, McElroy SL, et al. Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation. *Addiction*. 2008;103(4):687–694.
8. Oncken C, Arias AJ, Feinn R, et al. Topiramate for smoking cessation: a randomized, placebo-controlled pilot study. *Nicotine Tob Res*. 2014;16(3):288–296.
9. Kampman KM, Pettinati H, Lynch KG, et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2004;75(3):233–240.
10. Johnson BA, Ait-Daoud N, Wang XQ, et al. Topiramate for the treatment of cocaine addiction: a randomized clinical trial. *JAMA Psychiatry*. 2013;70(12):1338–1346.
11. Umbricht A, DeFulio A, Winstanley EL, et al. Topiramate for cocaine dependence during methadone maintenance treatment: a randomized controlled trial. *Drug Alcohol Depend*. 2014;140:92–100.
12. Johnson BA. Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings. *Biochem Pharmacol*. 2008;75(1):34–56.
13. French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety? *Ther Adv Drug Saf*. 2011;2(4):141–158.
14. McNamara JO. Pharmacotherapy of the Epilepsies. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. Chapter 21. New York, NY: McGraw-Hill; 2011.
15. Ray LA, Miranda R Jr, MacKillop J, et al. A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. *Exp Clin Psychopharmacol*. 2009;17(2):122–129.
16. Sobell L, Sobell M. Timeline followback: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. New York, NY: Humana Press; 1992:41–65.
17. Bender R. Calculating confidence intervals for the number needed to treat. *Control Clin Trials*. 2001;22(2):102–110.
18. Holden WL, Juhaeri J, Dai W. Benefit-risk analysis: a proposal using quantitative methods. *Pharmacoepidemiol Drug Saf*. 2003;12(7):611–616.
19. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med*. 1997;126(9):712–720.
20. Rösner S, Hackl-Herrwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2010;(12):CD001867.
21. Rösner S, Hackl-Herrwerth A, Leucht S, et al. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev*. 2010;(9):CD004332.
22. Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*. 2010;105(5):817–843.
23. Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238–1245.
24. Arroll B, Elley CR, Fishman T, et al. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev*. 2009;(3):CD007954.
25. Shabaruddin FH, Chen LC, Elliott RA, et al. A systematic review of utility values for chemotherapy-related adverse events. *Pharmacoeconomics*. 2013;31(4):277–288.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Addiction section. Please contact Daniel D. Langleben, MD, at dlangleben@psychiatrist.com.