Alcohol Dependence Treatments: Comprehensive Healthcare Costs, Utilization Outcomes, and Pharmacotherapy Persistence

Onur Baser, MS, PhD; Mady Chalk, PhD; Richard Rawson, PhD; and David R. Gastfriend, MD

Abstract

Objectives: To determine the healthcare costs associated with treatment of alcohol dependence with medications versus no medication and across the 4 medications approved by the US Food and Drug Administration (FDA).

Study Design: Retrospective claims database analysis.

Methods: Eligible adults with alcohol dependence were identified from a large US health plan and the IMS PharMetrics Integrated Database. Data included all medical and pharmacy claims at all available healthcare sites. Propensity score–based matching and inverse probability weighting were applied to baseline demographic, clinical, and healthcare utilization variables for 20,752 patients, half of whom used an FDA-approved medication for alcohol dependence. A similar comparison was performed among 15,502 patients treated with an FDA-approved medication: oral acamprosate calcium (n = 8958), oral disulfiram (n = 3492), oral naltrexone (NTX) hydrochloride (n = 2391), or extended-release injectable naltrexone (XR-NTX; n = 661). Analyses calculated 6-month treatment persistence, utilization, and paid claims for: alcoholism medications, detoxification and rehabilitation, alcohol-related and nonrelated inpatient admissions, outpatient services, and total costs.

Results: Medication was associated with fewer admissions of all types. Despite higher costs for medications, total healthcare costs, including inpatient, outpatient, and pharmacy costs, were 30% lower for patients who received a medication for their alcohol dependence. XR-NTX was associated with greater refill persistence and fewer hospitalizations for any reason and lower hospital costs than any of the oral medications. Despite higher costs for XR-NTX itself, total healthcare costs were not significantly different from oral NTX or disulfiram, and were 34% lower than with acamprosate.

Conclusion: In this largest cost study to date of alcohol pharmacotherapy, patients who received medication had lower healthcare utilization and total costs than patients who did not. XR-NTX showed an advantage over oral medications in treatment persistence and healthcare utilization, at comparable or lower total cost.

(Am J Manag Care. 2011;17:S222-S234)

For author information and disclosures, see end of text.

Alcohol consumption is the third leading actual cause of death in the United States[1]; however, among the top 25 diseases, patients with alcohol-use disorders are least likely to receive care that is based upon evidence-based practice.[2] The overall cost to the United States for alcohol-related illness was estimated at $184 billion in 1998[3]; payers spend an estimated $9.7 billion annually on direct treatment of these disorders.[4] Historically, over 70% of these costs has been spent by public systems[4]; however, this proportion is expected to increasingly shift to the private pay sector in coming years as a result of federal parity and health care legislative reform. With a national prevalence of alcohol dependence of 3.8%, or 7.9 million adults,[5] these morbidity, mortality, and cost burdens are driving efforts to develop the most clinically effective and resource-efficient evidence-based treatments possible.

The dominant mode of treatment of alcohol dependence is psychosocial treatment or counseling, and several models have shown evidence for effectiveness.[6] Although 4 medications have been approved by the US Food and Drug Administration (FDA) for the treatment of alcohol dependence, there is little adoption of these agents.[7,8] Survey results published in 2007 reported that pharmacotherapies for substance-use disorders (SUDs) were offered in less than 25% of public and private specialty treatment programs[7] and a 2007 study reported that SUD medications comprised less than 1% of all SUD treatment costs.[8] Nevertheless, the National Institute on Alcohol Abuse and Alcoholism has issued recommendations stating that medications are "helpful to patients in reducing drinking, reducing relapse to heavy drinking, achieving and maintaining abstinence, or a combination of these effects" and clinicians should "consider adding medication whenever [they] are treating someone with active alcohol dependence."[6]

There are multiple reasons why medication-assisted treatment (MAT) for alcohol dependence is not widely used, including long-standing traditions rooted in the mutual help movement, but adoption of MAT is also predicated on concerns about poor patient adherence to medication, modest efficacy, and poor cost-effectiveness.[9-11] Retrospective insurance database studies of oral medications have reported that 50% of patients fail to obtain their first refill,[12,13] and refill rates are worse for alcoholism medications

than for statins and psychiatric medications.[14] Clinical trials have found that medication adherence is crucial to efficacy.[15]

Medication adherence in substance-dependence treatment has been a priority concern of the National Institutes of Health for over 3 decades.[16] In 2006, the FDA approved the first extended-release formulation for the treatment of alcohol dependence, extended-release naltrexone (XR-NTX), which was designed to address the challenge of adherence through a once-monthly injection.[17] Of the 4 agents FDA-approved for the treatment of alcohol dependence studied in a retrospective claims analysis of commercial insureds, XR-NTX was associated with reduced estimated charges and utilization of inpatient detoxification days and alcoholism-related inpatient days, compared with all 3 oral agents (ie, oral naltrexone, disulfiram, and acamprosate calcium).[18] Given the importance of alcohol dependence treatment for public health and healthcare cost containment, the present study was designed to extend current knowledge of real-world effectiveness with alcohol dependence treatments, including treatment with no medication, any approved medication, and among the approved medications, treatment with each specific agent. This study sought to examine a larger cohort of insured patients treated with XR-NTX than previously studied, and to determine a comprehensive range of healthcare utilization and actual expended healthcare costs for each treatment category.

Methods

Data Sources and Study Population

This was a retrospective database analysis conducted using commercial enrollees from a large US health plan affiliated with i3 Innovus and the PharMetrics Integrated Database from 2005 to 2009. These databases included medical and pharmacy claims from all available healthcare sites (inpatient, hospital outpatient, emergency department [ED], physician's office, and surgery center) for virtually all types of provided services, including specialty, preventive office-based treatments, and retail and mail order pharmacy claims.

For the comparison of the "no medication" group to the "any medication" group, patients were required have at least 1 claim for alcohol dependence (*Diagnostic and Statistical Manual of Mental Disorders, 4th Edition,* code 303.xx) during the pre- or post-index period, have an alcohol use disorder diagnosis pre-index, and have at least 6 months of continuous enrollment pre-index and 6 months post-index. The earliest pharmacy claim for alcohol medication was set as the index date for the any medication group. The index date was defined as the first medical claim for a nonpharmacologic treatment such as a detoxification facility claim, a substance abuse treatment facility claim, or a substance abuse counseling claim. Patients in the nonpharmacologic substance group had no prescription fills for alcoholism medication while patients in the any medication group had at least 1 fill for any of the 4 alcoholism medications. Patients with liver failure during the pre-index period were excluded. Furthermore, patients were excluded if they had claims for pharmacological treatment in the month prior to the index date (with the exception of the XR-NTX group, because this group was occasionally required to demonstrate prior oral medication failure). These inclusion/exclusion criteria led to a final sample of 20,670 patients in the no medication group and 15,502 patients in the any medication group. **Figure 1** presents the sample sizes after applying the inclusion/exclusion criteria.

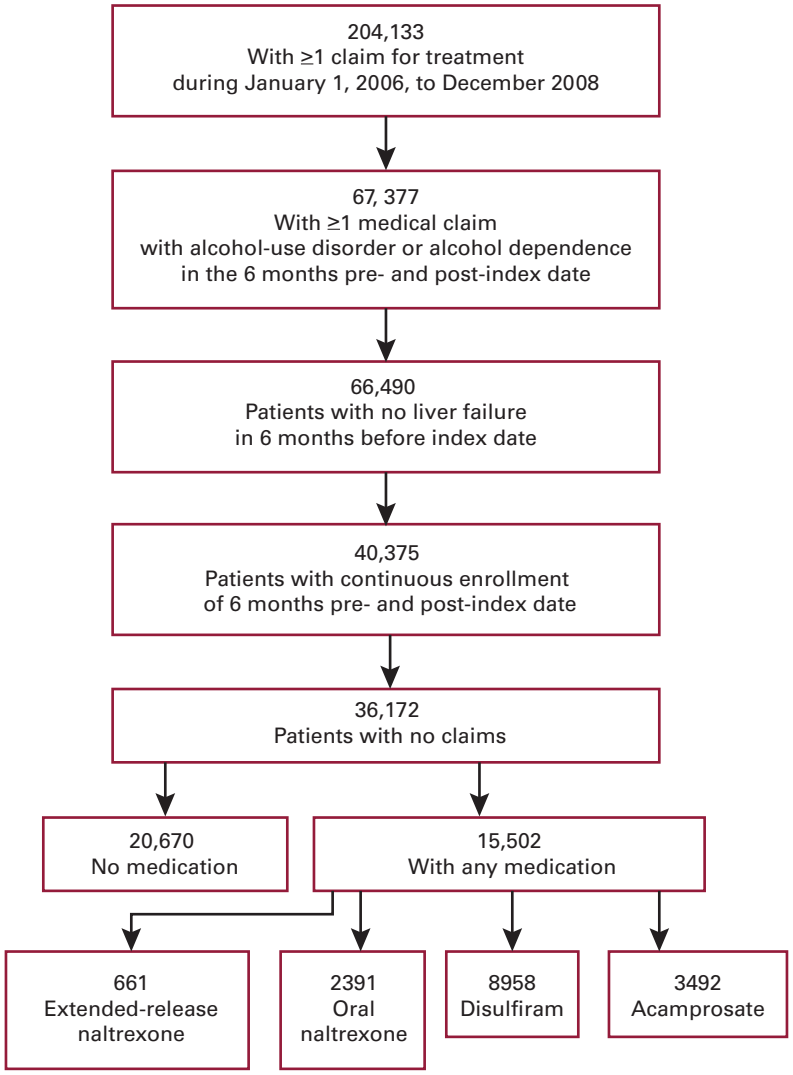
Similar criteria were required for patients in the comparison of the 4 alcoholism medications. Patients treated with XR-NTX were identified on the basis of an outpatient drug claim using the National Drug Code (NDC) or medical claims with the Healthcare Common Procedure Coding System code. The other medications, such as oral naltrexone, disulfiram, or acamprosate were identified using outpatient drug claims based on NDCs. The final sample of 661 patients in the XR-NTX group, 2391 patients in the oral NTX group, 8958 patients in the disulfiram group, and 3492 patients in the acamprosate group, was identified after applying the inclusion/exclusion criteria.

Statistical Analysis

We derived demographic and clinical characteristics of the study populations at baseline. In particular, age, sex, and geographic location were measured at the index date. Deyo-Charlson comorbidity score,[19] Elixhauser score,[20] and the number of distinct psychiatric diagnoses and medications were calculated during the pre-index period. The Deyo-Charlson comorbidity score is an *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* code adaption of the Charlson index, which assigns a range of weights, from 1 to 6 according to disease severity, for 19 conditions. The Elixhauser score is also a claims-based comorbidity index which sums a patient's comorbid conditions from among 30 *ICD-9-CM* comorbidity flags, differentiating secondary diagnoses from comorbidities by using diagnosis-related groups.

For socioeconomic status (SES), we constructed a summary measure for each US Zone Improvement Plan (ZIP) code using data on income, education, and occupation from the 2000 US Census and then linked this information to the patient's ZIP code of residence in the analytic files.[21] Factor analysis was used to identify 6 census variables that could be

Figure 1. Patient Selection Process



meaningfully combined into a summary socioeconomic status score. These variables included 3 measures of wealth/income (median household income, median value of housing units, and proportion of households with interest, dividend, or rental income), 2 measures of education (proportion of adult residents completing high school and college), and 1 measure of occupation/employment (proportion of employed residents with management, professional, and related occupations).[22]

Healthcare utilization and costs were calculated during both the pre-index and post-index periods. In terms of inpatient utilization, the number of detoxification facility days, and the number of detoxification and/or rehabilitation (admissions with an *ICD-9-CM* procedure for detoxification or rehabilitation), alcohol (admission with a principal diagnosis), and nonrelated inpatient admissions were measured. ED visits, alcohol-related physician visits, alcohol and substance abuse psychosocial provider visits, and non–alcohol-related outpatient visits were calculated. Utilization measures were presented per 1000 patients. Associated costs related to these measures and total costs were also calculated.

In addition to healthcare utilization and costs, we evaluated adherence by analyzing medication possession ratio and days of persistence with index medication refills post-index date.

Baseline characteristics were compared between the patient cohorts, and descriptive statistics were calculated as percentages and standard deviations. Differences between the cohorts were analyzed using the *t*-test, Mann-Whitney U test, and χ^2 test, and standardized differences were calculated. It has been demonstrated that standardized differences 10% and higher between the baseline variables are significant, and need to be adjusted to compare the outcome measures among the groups.[23,24]

Propensity-score matching was applied to compare the risk-adjusted outcomes between the no medication group and the any medication group. Propensity-score matching is a technique that aims at adjusting for selection bias in nonexperimental, nonrandomized, and retrospective studies like the present one.[25] By using propensity-score matching, each patient in the any medication group was "mirrored" by a patient with similar predefined characteristics in the no medication group. The following characteristics were used to match: age, sex, region, comorbid scores, SES, baseline healthcare utilization, and costs. Logistic regression was used to estimate propensity scores. Several interaction variables were constructed, but they were not determined to be significant. Estimation power of the logistic regression was determined by C statistics. Following the guidelines set forth by Baser, it was determined that one-to-one matching created the best balance among the groups.[26]

Following Imbens and Lechner, we applied propensity-score matching that accounts for multilevel treatments when comparing the 4 alcoholism medication groups.[27,28] Several applications of this method are presented in the medical literature.[29-31] The first step uses multinomial logistic regression

Table 1. Risk-Adjusted Baseline Characteristics of Alcohol-Dependent Patients With Any Versus No Medication

Pre-Index Period (6-month period before index date)	Alcohol-Dependent Patients (each group has N = 10,376) Any medication	No medication	
Continuous variables	**Mean (SD)**	**Mean (SD)**	***P***
Healthcare utilization			
Pre-index number of detox facility days (number of days/1000 patients)	79 (938)	65 (779)	.2366
Pre-index inpatient (number of admissions/1000 patients)			
Detoxification and/or rehabilitation	15 (147)	14 (135)	.5553
Alcohol-related inpatient admission	139 (436)	125 (427)	**.0244**
Non–alcohol-related inpatient admission	264 (607)	273 (632)	.2625
Pre-index outpatient (number of visits/1000 patients)			
Emergency department visit	734 (1968)	778 (2149)	.1236
Alcohol-related and physician provider	774 (3835)	487 (3110)	**<.0001**
Alcohol-related and substance abuse psychosocial provider	521 (3797)	374 (2585)	**.0011**
Non–alcohol-related outpatient admission	10,602 (11,063)	9846 (11,035)	**<.0001**
Costs (per patient)			
Pre-index inpatient			
Cost of detoxification and/or rehabilitation	$30 ($493)	$0 ($0)	**<.0001**
Cost of alcohol-related inpatient admission	$720 ($4315)	$650 ($3909)	.2224
Cost of non–alcohol-related inpatient admission	$2059 ($8297)	$2545 ($10,659)	**.0002**
Pre-index outpatient			
Cost of emergency department visit	$207 ($693)	$244 ($850)	**.0006**
Cost of alcohol-related and physician provider	$94 ($731)	$72 ($817)	**.0403**
Cost of alcohol-related and substance abuse	$50 ($355)	$25 ($259)	**<.0001**
Cost of non–alcohol-related outpatient admission	$21 ($25)	$20 ($27)	**.0107**
Pre-index pharmacy			
Cost of FDA-approved alcohol dependence medications	$5 ($45)	$0 ($0)	**<.0001**
Cost of other psychiatric medications	$122 ($427)	$62 ($307)	**<.0001**
Cost of nonpsychiatric medications	$361 ($899)	$247 ($806)	**<.0001**
Total cost (per patient = inpatient + outpatient + pharmacy)	$5922 ($11,439)	$6174 ($13,726)	.1519

FDA indicates US Food and Drug Administration.

to estimate conditional probabilities of being in the particular treatment group. The second and final step estimates conditional expectation of outcome given the treatment level. Adjusted Wald tests were performed to test for the difference in weighted characteristics across the treatment cohorts.

Statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, North Carolina) and STATA v10 (Stata Corp, College Station, Texas).

Results

The risk-adjusted pre-index characteristics of 10,376 patients matched between each of the 2 groups (any medication and no medication, respectively) showed the following similarities: age, (44.4 vs 44.5 years; *P* = not significant [NS]); sex (male, 61.8% vs 61.9%; *P* = NS); geographic region (Eastern, 18.4% vs 18.0%; *P* = NS); SES score (high SES, 29.2% vs 29.2%; *P* = NS); and pre-index severity (proxied by having a ≥3 Elixhauser Index score, 25.2% vs 25.1%; *P* = .06). Differences in the Deyo-Charlson comorbidity score (0.34 vs 0.38; *P* =.0002) and Elixhauser Comorbid conditions (1.63 vs 1.57; *P* = .0034) were significant, but in opposite directions. During the pre-index period, the number of distinct psychiatric diagnoses and medications were higher in patients in the any medication group compared with the no

medication group (2.71 vs 2.32 and 1.68 vs 1.29, respectively; both P <.0001).

Table 1 shows that, on average, detoxification admissions per 1000 patients in the any medication and no medication groups were similar (15 vs 14, respectively). Outpatient visits were significantly higher for patients in the any medication group. In particular, per 1000 patients, alcohol-related physician provider visits (774 vs 487) and non–alcohol-related outpatient visits (10,602 vs 9846) were significantly higher for the any medication group than the no medication group. The largest driver of pre-index treatment costs, however, was the cost of non–alcohol-related inpatient admission ($2059 vs $2545 per patient). After risk adjustment, the baseline costs in the any medication group were $5922 per patient versus $6174 per patient in the no medication group.

Table 2 presents the risk-adjusted outcome results. Patients in the no medication group stayed more days in detoxification facilities post-index relative to patients in the any medication group (3497 vs 483 days per 1000 patients). They had significantly more psychiatric diagnoses during the post-index period (3.19 vs 3.07). Post-index detoxification and/or rehabilitation admissions (563 vs 85), alcohol (660 vs 202), and nonalcohol (407 vs 257) admissions were significantly higher per 1000 patients in the no medication group. Higher admission days for the no medication group in detoxification and/or rehabilitation translated to a cost burden of $1350 versus $209 per patient in the any medication group. Costs for alcohol-related admissions were $2464 versus $801, and $2751 versus $2336 for non–alcohol-related inpatient admissions, respectively.

The pattern of greater utilization and costs also existed among patients in the no medication group for outpatient visits. This group was more likely to have physician provider visits (1970 vs 1454), psychosocial provider visits (1740 vs 991), and non–alcohol-related outpatient visits (14,101 vs 13,349) per 1000 patients. This translated into a greater cost burden of $106 per patient due to more physician provider visits and $61 due to more psychosocial provider visits. The 6-month total healthcare cost for a patient in the no medication group was $11,677 versus $8134 in the any medication group.

Among 15,502 patients who used any pharmacologic drug, 661 patients were treated with XR-NTX, 2391 with oral NTX, 3492 with disulfiram, and 8958 with acamprosate. Patients in the XR-NTX group were slightly older (45.91 years vs 44.24, P <.001; 43.53, P <.0001; 45.63, P = NS, respectively). There were no differences in the percentages of males in the groups (60% vs 58%, 62%, 59%; all P = NS). However, patients given XR-NTX resided more commonly in the East (34.0% vs 26%, 16%, 18%; all P <.0001) and South (31% vs 19%, 16%, 26%; all P <.01) compared with the Midwest and West. There was no clear pattern of SES differences among the 4 groups.

Table 3 presents the pre-index clinical, utilization, and cost characteristics of the 4 alcohol medication groups. In terms of severity (proxied by percentage with a ≥3 Elixhauser score) the XR-NTX group (31.0%) did not differ in high comorbidity rates relative to oral NTX (34.5%) or disulfiram (28.4%), but it was significantly lower compared with those given acamprosate (37.9%, P = .0004). However, patients in the XR-NTX group had a higher use of distinct psychiatric medication relative to the other groups. Compared with patients in the XR-NTX cohort, during the pre-index period, those receiving acamprosate had significantly more detoxification facility days, and those given disulfiram had significantly fewer. Also, the acamprosate group had more detoxification and/or rehabilitation admissions and alcohol- and non–alcohol-related admissions compared with those in the XR-NTX group. During the pre-index period, the number of non–alcohol-related outpatient visits was significantly higher in the XR-NTX group relative to others.

The total healthcare costs were significantly higher for patients in the XR-NTX group compared with those in the oral NTX and the disulfiram groups, but there were no differences in pretreatment costs between XR-NTX and acamprosate.

After adjusting for these baseline differences, the risk-adjusted outcome results for the 4 groups are presented in Table 4. Patients receiving XR-NTX had significantly higher refill adherence rates than patients in the other groups (21% vs 11% for oral NTX, 9% for disulfiram, and 6% for acamprosate). The number of persistence days was also significantly higher (61.6 days vs 49.8 days with oral naltrexone, 45.8 days with disulfiram, and 42.6 days with acamprosate) (Figure 2A). Patients receiving XR-NTX had a significantly lower number of distinct diagnoses relative to those given acamprosate (3.05 vs 3.30), and a lower number of psychiatric medications relative to those given disulfiram (1.96 vs 2.80).

Inpatient healthcare utilization in the XR-NTX group was significantly lower than that in the other groups. Patients given XR-NTX spent significantly fewer days in a detoxification facility relative to those given disulfiram or acamprosate (227 days vs 429 days vs 741 days per 1000 patients, respectively). Detoxification and/or rehabilitation admission and alcohol- and non–alcohol-related admission were significantly lower in the XR-NTX group relative to the other groups (P <.01) (Figure 2B). This translated

Table 2. Risk-Adjusted Outcomes in Alcohol-Dependent Patients With Any Versus No Medication

Post-Index Period (6 months after index date)	Alcohol-Dependent Patients (each group has N = 10,376)		
	Any medication	No medication	
Outcome	**Mean (SD)**	**Mean (SD)**	***P***
Post-index number of distinct psychiatric diagnoses	3.07 (1.78)	3.19 (1.71)	**<.0001**
Post-index number of distinct psychiatric medication	2.25 (1.83)	1.39 (1.56)	**<.0001**
Healthcare utilization			
Post-index number of detoxification facility days (number of days/1000 patients)	483 (2489)	3497 (7293)	**<.0001**
Post-index inpatient (number of admissions/1000 patients)			
Detoxification and/or rehabilitation	85 (336)	563 (641)	**<.0001**
Alcohol-related inpatient admission	202 (562)	660 (863)	**<.0001**
Non–alcohol-related inpatient admission	257 (650)	407 (757)	**<.0001**
Post-index outpatient (number of visits/1000 patients)			
Emergency department visit	787 (2352)	648 (2169)	**<.0001**
Alcohol-related and physician provider	1454 (5266)	1970 (6064)	**<.0001**
Alcohol-related and substance abuse psychosocial provider	991 (4425)	1740 (5781)	**<.0001**
Non–alcohol-related outpatient	13,349 (12,919)	14,101 (14,126)	**.0007**
Costs (per patient)			
Post-index inpatient			
Cost of detoxification and/or rehabilitation	$209 ($1140)	$1350 ($2863)	**<.0001**
Cost of alcohol-related inpatient admission	$801 ($3749)	$2464 ($7025)	**<.0001**
Cost of non–alcohol-related inpatient admission	$2336 ($12,492)	$2751 ($13,815)	**<.0001**
Post-index outpatient			
Cost of emergency department visit	$207 ($744)	$173 ($695)	**<.0001**
Cost of alcohol-related physician provider	$199 ($988)	$305 ($1204)	**<.0001**
Cost of alcohol-related substance abuse psychosocial provider	$87 ($440)	$148 ($605)	**<.0001**
Cost of non–alcohol-related	$25 ($29)	$27 ($32)	.0592
Post-index pharmacy			
Cost of FDA-approved alcohol dependence medications	$350 ($637)	$1 ($17)	**<.0001**
Cost of other psychiatric medications	$228 ($677)	$95 ($427)	**<.0001**
Cost of nonpsychiatric medications	$523 ($1153)	$291 ($967)	**<.0001**
Total cost (per patient = inpatient + outpatient + pharmacy)	$8134 ($15,887)	$11,677 ($19,889)	**<.0001**

FDA indicates US Food and Drug Administration.

to lower inpatient costs per patient for detoxification and rehabilitation (XR-NTX: $105 vs $192 with oral NTX, $203 with disulfiram, and $288 with acamprosate), alcohol-related inpatient admission (XR-NTX: $474 vs $618 with oral NTX, $874 with disulfiram, and $1166 with acamprosate), and non–alcohol-related admission (XR-NTX: $730 vs $1091 with oral naltrexone, $1498 with disulfiram, and $3885 with acamprosate).

Although outpatient healthcare utilization was similar across the groups, the average patient receiving XR-NTX had higher 6-month costs for ED visits ($272) vs oral agents ($227 with oral naltrexone, $227 with disulfiram, and $209 with acamprosate), and lower costs for alcohol-related physician provider visits (XR-NTX: $67 vs $107 oral NTX, $118 with disulfiram, and $291 with acamprosate) and alcohol and substance abuse outpatient visits (XR-NTX: $46 vs $76 with oral NTX, $114 with disulfiram, and $82 with acamprosate). XR-NTX was associated with higher costs for non–alcohol-related outpatient visits (NXT-XR: $4510 vs $3444 with oral NTX, $3194 with disulfiram, and $3589 with acamprosate).

Table 3. Baseline Characteristics of Alcohol-Dependent Patients by Pharmacotherapy

Pre-Index Period (6-month period before index date)	XR-NTX (n = 661)
Continuous variables	**Mean (SD)**
Clinical characteristics	
Pre-index Deyo-Charlson comorbidity score	0.41 (0.91)
Pre-index Elixhauser comorbid conditions	1.91 (1.71)
Pre-index number of distinct psychiatric diagnoses	3.20 (1.89)
Pre-index number of distinct psychiatric medication	2.00 (1.79)
Healthcare utilization	
Pre-index number of detoxification facility days number of days/1000 patients)	1212 (3802)
Pre-index inpatient (number of admissions/1000 patients)	
Detoxification and/or rehabilitation	215 (536)
Alcohol-related inpatient admission	380 (840)
Non–alcohol-related inpatient admission	333 (766)
Pre-index outpatient (number of visits/1000 patients)	
Emergency department visits	911 (2234)
Alcohol-related and physician provider	773 (3785)
Alcohol-related and substance abuse psychosocial provider	490 (2465)
Non–alcohol-related outpatient	12,470 (12,239)
Costs (per patient)	
Pre-index inpatient	
Cost of detoxification and/or rehabilitation	$688 ($2344)
Cost of alcohol-related inpatient admission	$1638 ($6032)
Cost of non–alcohol-related inpatient admission	$2504 ($8362)
Pre-index outpatient	
Cost of emergency department visits	$244 ($700)
Cost of alcohol-related and physician provider	$82 ($468)
Cost of alcohol-related and substance abuse psychosocial provider	$53 ($329)
Cost of non–alcohol-related	$25 ($27)
Pre-index pharmacy	
Cost of FDA-approved alcohol dependence medications	$100 ($174)
Cost of other psychiatric medications	$163 ($486)
Cost of nonpsychiatric medications	$553 ($1436)
Total cost (per patient = inpatient + outpatient + pharmacy)	$9467 ($13,988)

FDA indicates US Food and Drug Administration; NTX, naltrexone; XR-NTX, extended-release injectable naltrexone.

Post-index pharmacy costs were higher for the XR-NTX group; cost savings from inpatient and outpatient admissions, however, resulted in total costs that were significantly lower in patients given XR-NTX compared with those given acamprosate ($6757 vs $10,345 per patient). Significant differences in overall costs were not observed among the NXT-XR group and other groups.

Discussion

Access to the combined data from these 2 large insurance data sets allowed for the examination of clinical outcomes and costs/benefits associated with available types of alcoholism treatments (as employed in the US healthcare system), resulting in the largest health economic evaluation of alcoholism treatments reported to date in the literature.

Alcohol-Dependence Pharmacotherapy					
Oral NTX (n = 2391)		Disulfiram (n = 3492)		Acamprosate (n = 8958)	
Mean (SD)	*P*	Mean (SD)	*P*	Mean (SD)	*P*
0.33 (0.82)	**.0280**	0.33 (0.92)	**.0233**	0.40 (0.97)	.7860
2.04 (1.73)	.0850	1.74 (1.71)	**.0262**	2.17 (1.75)	**.0001**
3.14 (1.92)	.4632	2.91 (1.96)	**.0004**	3.08 (1.84)	.1228
1.78 (1.68)	**.0055**	1.73 (1.67)	**.0003**	1.70 (1.64)	**<.0001**
1376 (4169)	.3375	803 (2805)	**.0086**	1644 (3956)	**.0051**
226 (525)	.6384	165 (463)	**.0253**	294 (529)	**.0003**
350 (642)	.3997	313 (704)	.0553	469 (685)	**.0078**
377 (686)	.1775	297 (653)	.2553	412 (735)	**.0107**
810 (2055)	.2954	840 (2209)	.4560	772 (1993)	.1207
622 (3155)	.3486	1009 (4657)	.1582	657 (3346)	.4420
410 (5661)	.5933	782 (3643)	**.0107**	347 (2187)	.1468
11,359 (11,964)	**.0381**	10,877 (11,930)	**.0021**	10,757 (10,804)	**.0005**
$571 ($2000)	.2407	$313 ($1275)	**.0001**	$708 ($1890)	.8334
$1360 ($4333)	.2669	$1056 ($4452)	**.0183**	$1660 ($5759)	.9304
$2476 ($7975)	.9396	$2420 ($19,299)	.8555	$2619 ($9331)	.7336
$252 ($789)	.8013	$266 ($990)	.5018	$225 ($740)	.5050
$86 ($602)	.8563	$122 ($743)	.0740	$91 ($773)	.6581
$38 ($312)	.2870	$89 ($506)	**.0203**	$35 ($312)	.1620
$23 ($25)	**.0273**	$22 ($29)	**.0040**	$22 ($25)	**.0017**
$0 ($0)	**<.0001**	$0 ($0)	**<.0001**	$0 ($0)	**<.0001**
$145 ($525)	.4096	$109 ($394)	**.0069**	$114 ($398)	**.0118**
$373 ($854)	**.0021**	$308 ($838)	**<.0001**	$360 ($858)	**.0007**
$8031 ($12,113)	**.0165**	$6904 ($21,495)	**.0001**	$9543 ($118,914)	.9556

This risk-adjusted analysis compared 20,752 patients who received any versus no medication, and 15,502 patients who received 1 of the 4 FDA-approved medications. A total of 661 patients received treatment with XR-NTX, making this the largest sample studied to date with this particular treatment. In addition, the study involved a comprehensive analysis of actual total healthcare costs paid and healthcare service utilization. Results showed that, compared with alcohol dependence treatment that did not include medication, medication-assisted treatment was associated with significantly fewer admissions for detoxification and/or rehabilitation, alcohol-related inpatient medical care, and non–alcohol-related inpatient medical care. Costs for services in all of these inpatient categories were significantly lower in

Table 4. Risk-Adjusted Outcome Measures in Alcohol-Dependent Patients by Pharmacotherapy

	Alcohol-Dependence Pharmacotherapy						
Post-Index Period (6 months after index date)	**XR-NTX (n = 661)**	**Oral NTX (n = 2391)**		**Disulfiram (n = 3492)**		**Acamprosate (n = 8958)**	
Compliance and persistence with therapy	**%**	**%**	***P***	**%**	***P***	**%**	***P***
Continuous MPR ≥0.8	21	11	**<.0001**	9	**<.0001**	6	**<.0001**
Outcome	**Mean**	**Mean**	***P***	**Mean**	***P***	**Mean**	***P***
Persistence days with index medication	61.65	49.75	**.00**	45.81	**.00**	42.56	**.00**
Post-index number of distinct psychiatric diagnoses	3.05	2.94	.20	3.04	.89	3.30	**.04**
Post-index number of distinct psychiatric medications	1.96	1.98	.78	2.80	**.00**	2.10	.20
Healthcare utilization							
Post-index number of detoxification facility days (number of days/1000 patients)	227	361	.1442	429	**.0472**	741	**.0039**
Post-index inpatient (number of admissions/1000 patients)							
Detoxification and/or rehabilitation	43	76	**.0039**	98	**.0001**	120	**.0001**
Alcohol-related inpatient admission	82	184	**<.0001**	268	**<.0001**	317	**<.0001**
Non–alcohol-related inpatient admission	109	205	**<.0001**	250	**<.0001**	343	**<.0001**
Post-index outpatient (number of visits/1000 patients)							
Emergency department visits	903	817	.5017	823	.5604	809	.5742
Alcohol-related and physician provider	1053	1154	.7007	1140	.7543	1678	.1733
Alcohol-related and substance abuse psychosocial provider	705	999	.1940	1171	.0825	805	.6922
Non–alcohol-related outpatient	14,414	12,726	**.0086**	13,159	.0696	14,429	.9868
Cost (per patient)							
Post-index inpatient							
Cost of detoxification and/or rehabilitation	$105	$192	**<.0001**	$203	**<.0001**	$288	**<.0001**
Cost of alcohol-related inpatient admission	$474	$618	**<.0001**	$874	**<.0001**	$1166	**<.0001**
Cost of non–alcohol-related inpatient admission	$730	$1091	**<.0001**	$1498	**<.0001**	$3885	**<.0001**
Post-index outpatient							
Cost of emergency department visits	$272	$227	**.0007**	$227	**.0011**	$209	**.0001**
Cost of alcohol-related and physician provider	$67	$107	**<.0001**	$118	**<.0001**	$291	**<.0001**
Cost of alcohol-related and substance abuse psychosocial provider	$46	$76	**<.0001**	$114	**<.0001**	$82	**<.0001**
Cost of non–alcohol-related	$4510	$3444	**<.0001**	$3194	**<.0001**	$3589	**.0008**
Post-index pharmacy							
Cost of FDA-approved alcohol dependence medications	$2230	$200	**<.0001**	$209	**<.0001**	$292	**<.0001**
Cost of other psychiatric medications	$326	$232	**<.0001**	$168	**<.0001**	$229	**<.0001**
Cost of nonpsychiatric medications	$600	$477	**<.0001**	$417	**<.0001**	$537	.1160
Total cost (per patient = inpatient + outpatient + pharmacy)	$6757	$6595	.6431	$7107	.3601	$10,345	**<.0001**

FDA indicates US Food and Drug Administration; MPR, medication possession ratio; NTX, naltrexone; XR-NTX, extended-release injectable naltrexone.

patients who received a medication, and (despite significantly higher costs for medications) total healthcare costs, including inpatient, outpatient, and pharmacy costs, were 30% lower for patients who received a medication for their alcohol dependence. With XR-NTX, cost data associated with hospital admissions and stays reflected a similar picture. Hospital costs for patients receiving XR-NTX were significantly and substantially lower than those for patients receiving 1 of the 3 oral medications. Patients given XR-NTX used fewer days in detoxification and had fewer admissions to the hospital for any reason than patients given 1 of the 3 oral medications.

Costs for services in all of these inpatient categories were significantly lower for patients who received XR-NTX, and despite significantly higher costs for XR-NTX, total healthcare costs, including inpatient, outpatient, and pharmacy costs, were not significantly different from total costs with oral NTX or disulfiram, and were 34% lower than with acamprosate.

The frequency of hospital admission is an intensive utilization and cost-related variable and may also represent a proxy for morbidity, in the absence of direct clinical data (which is lacking with retrospective claims data such as these). As such, reduced hospitalization, which is obviously important in cost reduction, is also an important objective in its own right. For example, medication was associated with 30% lower costs than no medication treatment; compared with no medication treatment, the relative risk reduction associated with medication was 85% for admission to detoxification or rehabilitation, and 69% for alcohol-related admission. Among the 4 medications, total costs with XR-NTX were not significantly different from oral NTX and disulfiram, and they were 34% lower than those with acamprosate. XR-NTX was associated with relative risk reductions for admission to detoxification/rehabilitation of 43% versus oral NTX, 56% versus disulfiram, and 64% versus acamprosate, and reductions for admission to alcohol-related hospitalization of 55% versus oral NTX, 69% versus disulfiram, and 74% versus acamprosate.

These reductions showed an inverse association with refill persistence (Figure 2A). One of the most important challenges in the use of alcohol pharmacotherapies is retaining patients in treatment (on medication) for clinically adequate durations. In the 2 measures of treatment duration, participants receiving XR-NTX were retained significantly longer and more continuously on medication than participants receiving oral medications. Of the 4 agents, the 2 compliance parameters, persistence (days with index medication) and continuous mean possession ratio greater than 80% of days, both showed a similar pattern (in increasing order of persistence): acamprosate, disulfiram, oral NTX, and XR-NTX. This pattern closely follows the burden of medication administration: acamprosate, 2 tablets 3 times daily; disulfiram and oral NTX, 1 tablet once daily (oral NTX is sometimes given in higher doses every other day); and XR-NTX, 1 injection per month. Also, the pattern of persistence is opposite the rate of admissions with the 4 medications (Figure 2B).

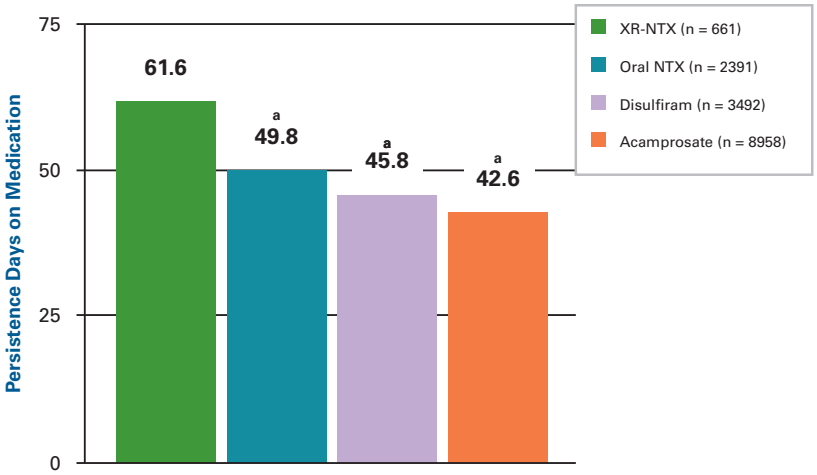
The cost differences found in these comparisons are revealing, because the group treated with any medication had overall medication costs that were more than double the medication costs (ie, nonalcoholism medications) of those with no alcoholism medications. Yet, their total healthcare costs were less. Similarly, the cost of XR-NTX alone was up to 10-fold higher than that for the oral alcohol dependence agents (some of which are available as generic products). Total healthcare costs, however, were either associated with no difference or lower expense. This finding suggests that the cost of a particular treatment should not be confused with the overall cost of care and that the overall objective of quality and efficient healthcare needs to transcend the compartmentalization of costs within pharmacy benefit management versus overall healthcare management.

These patients, in general, also had psychiatric and other medical comorbidities. The reasons for the higher cost of psychiatric and other medication are not clear. Physicians who use alcoholism pharmacotherapies may be more familiar with appropriate diagnosis and treatment of concurrent psychiatric and medical conditions. Also, because the any medication group spent less time in the hospital, effective outpatient management may have necessitated more aggressive use of outpatient medications.

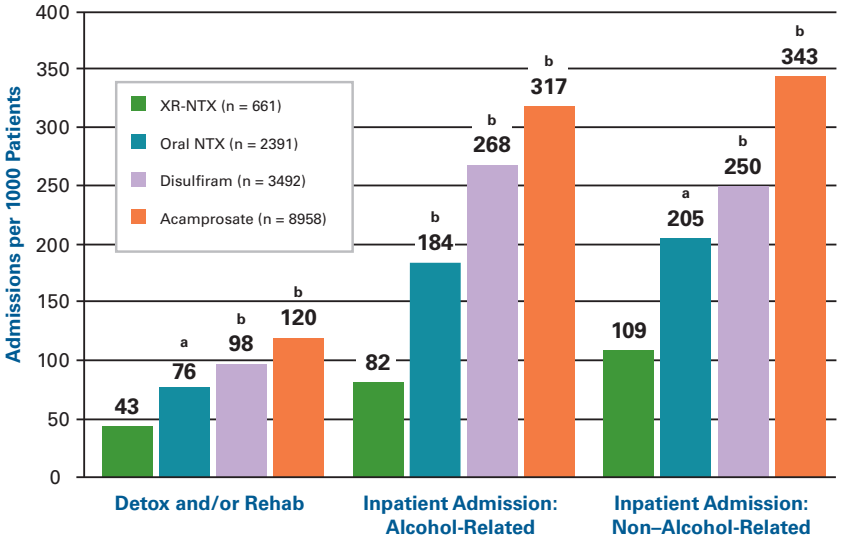
Retrospective claims analyses such as these have a number of limitations. Because the study design did not include random assignment to the any versus no medication conditions, nor to specific medication conditions, the findings represent associations, but not necessarily causality. The cohorts may have had unobserved differences in baseline characteristics; for example, patient motivation or healthcare service quality (eg, physician knowledge and training, psychosocial treatment methods used), so that the precise contribution of medication or type of medication cannot be definitively determined. Because there were no quantitative measures of baseline alcohol use, comparability of the participants' alcohol-use disorder severity across treatment conditions could not be ensured. Similarly, the absence of these baseline data make it impossible to compare reduction in alcohol quantity or frequency across conditions, a commonly used outcome measure in treatment outcome research. No data

Figure 2. Alcohol Dependence Pharmacotherapies: Health Economic Outcomes 6 Months After Index Date

A. Persistence Days on Medication



B. Inpatient Admissions per 1000 Patients



NTX indicates naltrexone; XR-NTX, extended-release injectable naltrexone.
[a] $P < .01$ vs XR-NTX.
[b] $P < .001$ vs XR-NTX.

are available regarding adverse events, which are important considerations, given that medications are known to have side effects, some of which are associated with boxed warnings on the prescribing information, and these differ between the oral and the injectable agents. Also, the time frame for outcomes was limited to 6 months and the samples consisted of commercial insureds as opposed to Medicaid or uninsured patients. Furthermore, the XR-NTX sample was smaller than the others (because it is the most recently introduced agent), subject inclusion was limited to patients with 1 year of continuous enrollment (which could omit those who lost insurance due to job loss), no information was available as to the recommended or adequate duration of treatment, and oral medication adherence was only indirectly measured through

prescription refills (therefore no information was available to confirm that patients took their oral medications).

Despite these limitations, the study has some relevant strengths. Baseline data (Table 2), with propensity-score matching and inverse probability weighting across a number of demographic, clinical, and utilization variables, demonstrated good comparability between the any versus no medication cohorts. The analysis showed robust findings in healthcare cost and utilization domains, a major strength that mitigates the limitation of not having alcohol consumption data. Although the average treatment duration was 2 to 3 months, meaningful outcomes were detected over a 6-month time frame, indicating that treatment benefits may outlast the active treatment phase. The patterns observed with medication adherence, hospital utilization, and costs demonstrated a high degree of internal consistency. External validity was also strong, given the relatively large sample sizes composed of real-world patients treated by community providers and given conventional treatment.

These findings are compatible with real-world evaluations of alcohol pharmacotherapy refill persistence.[12-14,17] Three prior analyses of pharmacy claims for oral NTX refills have shown that as few as half of patients obtain the first refill, and most do not complete a reasonable course of treatment.[12-14] One of these studies found significantly lower refill rates for oral alcohol pharmacotherapies than for statins, antidepressants, and antipsychotics,[14] and another found that refill failure was associated with significantly more detoxifications and hospital admissions.[13]

More recently, a retrospective claims analysis in NJ Blue Cross Blue Shield insureds found that although medication persistence remains an issue, XR-NTX was associated with significant reductions in cost due to alcohol-related hospitalizations, total medical costs, and total pharmacy costs (see the article by Jan et al in this supplement).[32] A study of AETNA beneficiaries showed that patients given XR-NTX persisted with treatment longer than those given oral medications, and XR-NTX was associated with decreased inpatient and emergency healthcare costs and utilization to a greater extent than patients receiving 1 of the 3 oral agents (see the article by Bryson et al in this supplement).[33]

Mark et al also analyzed retrospective commercial claims between any versus no medication, and among the 4 FDA-approved alcoholism medications. They determined that medication was associated with less detoxification and alcoholism-related inpatient care. That study also showed a similar pattern among the 4 medications; increased burden of medication administration (acamprosate >oral NTX or disulfiram >XR-NTX) was associated with decreased refill persistence. The XR-NTX cohort used 224 detoxification days per 1000 patients (vs 227 in the present study) and was associated with the fewest days for detoxification or alcohol-related hospitalizations among the 4 agents.[18] The present study replicates those findings and extends them, because the earlier study consisted of a single data source (examining 5954 matched cases in the any vs no medication comparison and 295 patients given XR-NTX) and used estimated charges and calculated these for only detoxification and alcohol-related inpatient admissions, whereas the present study combined 2 large data sources (examining 20,752 overall cases and 661 patients given XR-NTX) and calculated actual expended dollars for all healthcare costs, including the costs of the agents.

The relationships between use of medications, counseling, and utilization/cost outcomes suggested in these data are intriguing and raise important questions for further research. Although this study confined its cost evaluation to healthcare expenditures, society bears additional costs from alcohol dependence, due to deterioration, absenteeism and loss in the workforce, damage to property and life, and court proceedings and incarceration in the justice system. These costs are worthy of future analysis as well. Effectiveness findings with medication-assisted treatment that takes these aggregate burdens into account have led to implementation strategies in the public sector.[34] The National Quality Forum issued a statement in 2007 that "pharmacotherapy should be a standard component of treatment for SUD [substance use disorders]" [35] and efforts to increase pharmacotherapy use and design performance measures are under way.[36] Effective treatment with medication, and particularly the most effective pharmacologic therapy, is an opportunity that continues to warrant research, education, and implementation initiatives from healthcare systems, insurers, and policymakers.

Author affiliations: STATinMED Research and the University of Michigan (OB); Treatment Research Institute (MC); University of California, Los Angeles (RR); Alkermes, Inc (DRG).

Funding source: This study was funded through a contract from Alkermes, Inc to Ingenix Pharmaceutical Services Inc and STATinMED Research, Inc.

Author disclosures: Dr Gastfriend is an employee of Alkermes, Inc and reports owning stock in the company. Dr Baser, Dr Chalk, and Dr Rawson report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship information: Concept and design (MC, RR, DRG); acquisition of data (OB); analysis and interpretation of data (OB, MC, RR, DRG); drafting of the manuscript (OB, MC, RR, DRG); critical revision of the manuscript for important intellectual content (MC, RR, DRG); statistical analysis (OB); obtaining funding (DRG); and administrative, technical, or logistic support (DRG).

Address correspondence to: David R. Gastfriend, MD, 852 Winter St, Waltham, MA 02139. E-mail: david.gastfriend@alkermes.com.

REFERENCES

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000 [published correction appears in *JAMA*. 2005;293(3):293-294, 298]. *JAMA*. 2004;291(10):1238-1245.

2. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348 (26):2635-2645.

3. Harwood H; The Lewin Group. Updating estimates of the economic costs of alcohol abuse in the United States: estimates, update methods, and data. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 2000.

4. Mark TL, Coffey RM, McKusick DR, et al. National estimates of expenditures for mental health services and substance abuse treatment, 1991-2001 SAMHSA Publication No. SMA 05-3999. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.

5. Grant BF, Dawson DA, Stinson FS, et al. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend*. 2004;74:223-234.

6. National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, US Department of Health and Human Services. Helping patients who drink too much: a clinician's guide. Updated 2005 edition. http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm. Published May 2007. Accessed June 1, 2011.

7. Knudsen HK, Ducharme LJ, Roman PM. The adoption of medications in substance abuse treatment: associations with organizational characteristics and technology clusters. *Drug Alcohol Depend*. 2007:87:164-174.

8. Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend*. 2009; 99(1-3):345-349.

9. Mark TL, Kranzler HR, Song X. Understanding US addiction physicians' low rate of naltrexone prescription. *Drug Alcohol Depend*. 2003;71:219-228.

10. Mark TL, Swait J. Using stated preference modeling to forecast the effect of medication attributes on prescriptions of alcoholism medications. *Value Health*. 2003;6:474-482.

11. Thomas CP, Wallack SS, Lee S, et al. Research to practice: adoption of naltrexone in alcoholism treatment. *J Subst Abuse Treat*. 2003;24:1-11.

12. Harris KM, DeVries A, Dimidjian K. Datapoints: trends in naltrexone use among members of a large private health plan [news column]. *Psychiatr Serv*. 2004;55(3):221.

13. Kranzler HR, Stephenson JJ, Montejano L, Wang S, Gastfriend DR. Persistence with oral naltrexone for alcohol treatment: implications for health-care utilization. *Addiction*. 2008;103(11):1801-1808.

14. Hermos JA, Young MM, Gagnon DR, Fiore LD. Patterns of dispensed disulfiram and naltrexone for alcoholism treatment in a veteran patient population. *Alcohol Clin Exp Res*. 2004;28(8):1229-1235.

15. Pettinati HM, Volpicelli JR, Pierce Jr, JD, O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of Addictive Diseases*. 2000;19(1):71-83.

16. Willette R, ed. Narcotic antagonists: the search for long-acting preparations. 1976. *Natl Inst Drug Abuse Res Monogr Ser.* Rockville, MD.

17. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Ann NY Acad Sci*. 2011;1216(1):144-166.

18. Mark TL, Montejano L, Kranzler HR, Chalk M, Gastfriend DR. Comparison of healthcare utilization and costs among patients treated with alcohol dependence medications. *Am J Manag Care*. 2010;16(12):879-888.

19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

20. Elixhauser A, Steiner C, Harris D, Coffey R. Comorbidity measures for use with administrative data. *Medical Care*. 1998; 36(1):8-27.

21. Roux A, Merkin S, Arnett D, et al. Neighborhood of residence and incidence of coronary heart disease. *New Engl J Med*. 2001; 345(2):99.

22. Birkmeyer N, Gu N, Baser O, Morris A, Birkmeyer J. Socioeconomic status and surgical mortality in the elderly. *Medical Care*. 2008;46(9):893.

23. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med*. 2006;25(12):2084-2106.

24. Baser O. Choosing propensity score matching over regression adjustment for causal inference: when, why and how it makes sense. *J Med Econ*. 2007;10:379-391.

25. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127(8 Pt 2):757-763.

26. Baser O. Too much ado about propensity score models? comparing methods of propensity score matching. *Value Health*. 2006;9(6):377-385.

27. Imbens GW. The role of the propensity score in estimating dose-response functions. *Biometrika*. 2000;87(3):706-710.

28. Lechner M. Identification and estimation of causal effects of multiple treatments under the conditional independence assumption (September 1999). http://ssrn.com/abstract=177089. Accessed June 1, 2011.

29. Wang J, Donnan PT, Steinke D, MacDonald TM. The multiple propensity score for analysis of dose-response relationships in drug safety studies. *Pharmacoepidemiol Drug Saf*. 2001;10(2): 105-111.

30. Foster EM. Propensity score matching: an illustrative analysis of dose response. *Medical Care*. 2003;41(10):1183-1192.

31. Baser O. Propensity score matching with multi-level categories: an application. *Ispor Connections*. 2008;14(2):4-8.

32. Jan S, Gill P. Utilization patterns of extended-release naltrexone for alcohol dependence. *Am J Manag Care*. 2011;17(8): S210-S212.

33. Bryson WC, McConnell KJ, Korthuis PT, McCarty D. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. *Am J Manag Care*. 2011,17(8): S213-S221.

34. Missouri requires providers to offer medication-assisted treatment. *Alcoholism & Drug Abuse Weekly*. 2009;21;3-4.

35. National Quality Forum (2007). Evidence-based treatment practices for substance use disorders. Washington, DC: National Quality Forum.

36. Thomas CP, Garnick DW, Horgan CM, et al. Advancing performance measures for use of medications in substance abuse treatment. *J Subst Abuse Treat*. 2011;40(1):35-43.