Comparison of Healthcare Utilization Among Patients Treated With Alcoholism Medications

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Objectives: To determine in a large claims database the healthcare utilization and costs associated with treatment of alcohol dependence with medications vs no medication and across 4 US Food and Drug Administration (FDA)–approved medications.

Study Design: Claims database analysis.

Methods: Eligible adults with alcohol dependence claims (n = 27,135) were identified in a commercial database (*MarketScan*; Thomson Reuters Inc, Chicago, Illinois). Following propensity score–based matching and inverse probability weighting on demographic, clinical, and healthcare utilization variables, patients who had used an FDA-approved medication for alcohol dependence (n = 2977) were compared with patients who had not (n = 2977). Patients treated with oral naltrexone hydrochloride (n = 2064), oral disulfiram (n = 2076), oral acamprosate calcium (n = 5068), or extended-release injectable naltrexone (naltrexone XR) (n = 295) were also compared for 6-month utilization rates of alcoholism medication, inpatient detoxification days, alcoholism-related inpatient days, and outpatient services, as well as inpatient charges.

Results: Patients who received alcoholism medications had fewer inpatient detoxification days (706 vs 1163 days per 1000 patients, $P<.001$), alcoholism-related inpatient days (650 vs 1086 days, $P<.001$), and alcoholism-related emergency department visits (127 vs 171, $P=.005$). Among 4 medications, the use of naltrexone XR was associated with fewer inpatient detoxification days (224 days per 1000 patients) than the use of oral naltrexone (552 days, $P=.001$), disulfiram (403 days, $P=.049$), or acamprosate (525 days, $P<.001$). The group receiving naltrexone XR also had fewer alcoholism-related inpatient days than the groups receiving disulfiram or acamprosate. More patients in the naltrexone XR group had an outpatient substance abuse visit compared with patients in the oral alcoholism medication groups.

Conclusion: Patients who received an alcoholism medication had lower healthcare utilization than patients who did not. Naltrexone XR showed an advantage over oral medications in healthcare utilization and costs.

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For author information and disclosures, see end of text.

Alcohol use disorders (AUDs), including alcohol abuse and dependence, occur commonly in the general population, with an estimated 12-month prevalence of 8.46%.[1] Alcohol abuse and dependence are associated with a range of adverse medical, psychiatric, family, legal, and work-related problems. Although alcoholism is a leading cause of preventable death in the United States,[2] evidence-based treatment of AUDs is not commonly used.[3] Since 2005, the National Institute on Alcohol Abuse and Alcoholism[4] has recommended that medication should be considered for every patient with alcohol dependence. In practice, few patients with alcohol dependence are prescribed medications approved by the US Food and Drug Administration (FDA) to treat the disorder.[5] Moreover, among patients who are prescribed such medication, adherence is low, which significantly reduces efficacy.[6-10]

In part, the reluctance of physicians to prescribe alcoholism medications and of patients to take the medications stems from skepticism about their efficacy.[11] Comparative effectiveness investigations, particularly comparing alcoholism medication treatment with standard care, are needed to address this information gap. Efficacy studies[12-15] using randomized controlled trial (RCT) designs have found that pharmacotherapy is superior to psychosocial treatment alone. However, there are inconsistencies in results across studies, with large multisite RCTs failing to meet their specified end points for disulfiram,[16] oral naltrexone hydrochloride,[17] and acamprosate calcium.[18] Furthermore, where efficacy trials have shown positive findings, results have demonstrated only modest effects.[15]

Information is also needed to compare the relative efficacy of existing alcoholism medications, particularly their ability to address the problem of poor adherence. There are 4 FDA-approved medications for the treatment of alcohol dependence. Disulfiram, an aversive agent, acts as a deterrent to drinking.[16] Naltrexone is an opioid antagonist and is thought to reduce the rewarding effects of alcohol.[19] Acamprosate is believed to reduce the risk of relapse by stabilizing glutamatergic pathways in individuals during the postwithdrawal phase.[20] First approved as an oral treatment, naltrexone was subsequently approved also as an extended-release injectable suspension (naltrexone XR). In contrast to oral naltrexone, disulfiram,

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Take-Away Points

Retrospective comparisons among similar patients taking any alcoholism medication vs no alcoholism medication and among similar patients taking 1 of 4 alcoholism medications found the following:

- Filling a prescription for alcoholism medication was associated with fewer inpatient detoxification days, alcoholism-related inpatient days, and alcoholism-related emergency department visits.
- Using extended-release naltrexone hydrochloride was associated with fewer inpatient detoxification days and fewer alcoholism-related inpatient days compared with using oral naltrexone, disulfiram, or acamprosate calcium.

and acamprosate, which require daily dosing, naltrexone XR is administered as a monthly injection. Because naltrexone XR was designed to enhance patient adherence, comparison of the effect of that formulation vs oral medications on treatment outcomes is of considerable interest.[21]

Although RCTs are an important source of information on comparative effectiveness, they pose obstacles to external validity that limit their applicability to clinical practice. These include enrollment that favors highly motivated patients, compliance-inducing pill accounting procedures, unblinding because of adverse events, and assessment reactivity in research subjects.[22,23] In contrast to data from RCTs, observational studies can reflect the experiences of a broad sample of patients with alcoholism who receive care in naturalistic settings. In particular, retrospective analysis of large data sets (such as those composed of insurance claims) does not impose artificially constrained treatment frequencies, fixed duration of treatment, visits with nonprovider research assistants, or incentives for participation. In addition, providers of services detailed in these data sets represent the full spectrum of disciplines and settings that exist in the real world. These features favor generalizability. The main drawback of observational data is the potential for selection bias, which may be addressed with statistical controls.

This study evaluated approved treatments for alcohol dependence in a naturalistic population using a 2-stage approach. First, we compared the use of any of the FDA-approved medications vs no medication treatment. Second, we compared 4 alcoholism medications with one another relative to treatment persistence and healthcare utilization and cost outcomes.

METHODS

Data were obtained from the Thomson Reuters *MarketScan* Commercial Claims and Encounter database that comprises enrollment information and medical and prescription medication claims from approximately 150 large self-insured employers and regional health plans located throughout the United States (yielding approximately 25 million individuals per year). The contributors to the database provide insurance coverage under various fee-for-service and capitated health plans, including preferred provider organizations, indemnity plans, and health maintenance organizations.

For comparison of patient groups receiving any vs no alcoholism medication, the index date was defined as the earliest date of utilization of 1 of 4 alcoholism medications or as the alcohol dependence diagnosis date for the group receiving no alcoholism medication. Patients in the latter group had no prescription fills for an alcoholism medication, while patients in the group receiving any alcoholism medication had at least 1 fill for any of 4 alcoholism medications. Patients were required to be 18 years or older and to have at least 6 months of continuous enrollment before the index date and 6 months after the index date. Patients were required to have at least 1 claim for alcohol dependence (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*] code 303.xx) during the pre–index date or post–index date periods and to have a diagnosis of alcohol dependence or abuse (*DSM-IV* code 303.xx or 305.xx) before the index date. The study required an alcohol dependence diagnosis to be consistent with the labeled indication for the medications. A preperiod alcohol dependence or abuse diagnosis was required for the analysis of any vs no alcoholism medication use, as otherwise it would be likely that the group receiving no alcoholism medication would be earlier in their treatment course than the group receiving any alcoholism medication. These inclusion and exclusion criteria led to final samples of 4047 patients in the group receiving any alcoholism medication and 4730 patients in the group receiving no alcoholism medication. **eAppendix A** (available at **www.ajmc.com**) gives sample sizes after applying each inclusion or exclusion criterion.

Patients in the comparison of 4 alcoholism medications were required to have 6 months of continuous enrollment before the index date and after the index date and to be 18 years or older. Patients treated with oral naltrexone, disulfiram, or acamprosate were identified using outpatient drug claims based on national drug codes. The index date was defined as the earliest utilization date of 1 of 4 medications. Patients treated with naltrexone XR were identified on the basis of an outpatient drug claim with a national drug code for naltrexone XR or a medical claim with a Healthcare Common Procedure Coding System code for naltrexone XR. The earliest such claim was set as the index date. The following numbers of patients from the database met the study criteria: 295 for

naltrexone XR, 2064 for oral naltrexone, 2076 for disulfiram, and 5068 for acamprosate.

Drug utilization patterns and other outcomes were measured during the first 6 months following the index date. Naltrexone XR utilization amounts were calculated by determining the number of unique service dates (ie, injections) for naltrexone XR and multiplying those unique days by 30.5 days (the mean number of days per month in a year) to derive the total days a patient was receiving naltrexone XR. The total number of days of receiving naltrexone XR was then divided by 180 days to determine the percentage of time over 6 months that the patient was receiving naltrexone XR. For the oral agents, the percentage of days with medication fills was determined by adding the days supplied indicated on each prescription drug claim and dividing by 180 days.

The following inpatient utilization outcomes were examined: detoxification admissions (admissions with an *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code for detoxification), alcoholism-related admissions (admissions with a principal diagnosis of alcohol dependence), and nonalcoholism-related admissions. Utilization was measured as the percentage of patients with admissions and the total inpatient days. Emergency department (ED) utilization was captured as the percentage of patients visiting an ED and the number of alcoholism-related ED visits. Outpatient behavioral health services utilization was captured as the percentage of patients having visits with a primary diagnosis of substance abuse or a combined substance abuse and mental health diagnosis. We also measured the occurrence of diagnoses of schizophrenia, bipolar disorder, depression, and anxiety disorder. Finally, we measured costs for inpatient detoxification days and alcoholism-related admissions by multiplying charges per day by the number of inpatient detoxification days or alcoholism-related inpatient days.

Charges for inpatient treatment were determined using the Healthcare Cost and Utilization Project National Inpatient Sample (NIS) data set (http://hcupnet.ahrq.gov/). The NIS is the largest all-payer inpatient care database in the United States. The sampling frame for the 2008 NIS is a hospital sample that comprises approximately 90% of all hospital discharges in the United States. Charge information is provided on all patients, regardless of payer, including persons covered by Medicare, Medicaid, and private insurance, as well as the uninsured. For this study, charges were used for patients with private insurance having a principal diagnosis of alcohol dependence.

We used propensity score–based matching and inverse probability weighting to reduce the potential for cohort selection bias. We developed propensity scores using a logit model to compare the groups receiving any vs no alcoholism medication. Explanatory variables were selected based on their hypothesized confounding relationship with the outcome variables and included the following: (1) sex, (2) percentage of college graduates in the patient's zip code, (3) log of the median household income in the patient's zip code, (4) geographic region, (5) relationship to employee (employee, spouse, or child or dependent), (6) preperiod comorbidity burden measured using the Charlson Comorbidity Index,[24] and (7) the chronic disease score.[25] The following preperiod measures were also included: (8) comorbid psychiatric diagnosis, (9) AUD diagnosis, (10) drug abuse or dependence diagnosis, (11) detoxification admission, (12) alcoholism-related admission, and (13) nonalcoholism-related admission. Propensity scores were calculated as the predicted probability of being in the group receiving any alcoholism medication given the demographic, geographic region, and clinical factors listed. A nearest neighbor matching with a 1:1 matching ratio was used to match the 2 groups based on their scores. The balancing of variables was examined using standardized difference (threshold of 10), paired *t* test (for continuous variables), or McNemar test (for dichotomous variables). The matched sample comprised 2977 patients each in the group receiving any alcoholism medication and the group receiving no alcoholism medication.

Inverse probability of treatment weighting (IPTW) was used to adjust for differences in the characteristics of the 4 alcoholism medication groups being compared. To estimate the IPTW, a multinomial logit model was used in which the dependent variable was the treatment group. The independent variables were the demographic, geographic region, and clinical factors already listed. The IPTW was calculated as the inverse of the predicted conditional probability of being in the particular treatment group. The IPTW was normalized by its mean and was applied to the data to generate a reweighted pseudopopulation. Adjusted Wald test was performed to test for the difference in weighted continuous characteristics across the treatment cohorts. Rao-Scott χ^2 test was conducted to test for the difference in the distribution of discrete outcomes across groups. STATA 9.2 MP (StataCorp LP, College Station, Texas) was used in the analyses.

RESULTS

Comparison of Groups Receiving Any vs No Alcoholism Medication

A total of 27,135 eligible adults were identified in the commercial database. Table 1 gives characteristics of 2977 matched patients in the group receiving any alcoholism medication and the group receiving no alcoholism medication. Approximately 60 percent of patients were male, with a mean

Table 1. Characteristics of Propensity Score–Matched Patients in the Groups Receiving Any vs No Alcoholism Medication

Characteristic	Receipt of Alcoholism Medication		
	Any (n = 2977)	None (n = 2977)	*P* Value
Male sex, %	61.5	62.5	.50
Age group, y, %			
18-34	16.6	16.6	.97
35-44	26.7	25.6	.31
45-54	35.8	36.4	.62
55-64	21.0	21.5	.63
Geographic region, %			
Northeast	13.4	13.6	.82
North central	36.9	36.1	.53
South	29.0	29.2	.86
West	20.7	21.0	.79
Relationship to employee, %			
Self	61.6	61.4	.87
Spouse or partner	32.0	32.5	.68
Child or dependent	6.3	6.0	.61
Neighborhood characteristics			
Median household income, mean (SD), $	50,836 (17,239)	50,623 (16,901)	.62
% Below poverty level	9.1	9.2	.84
% African American	9.4	9.7	.48
% College graduate	27.0	27.0	.97
Preperiod psychiatric comorbidity diagnoses			
% With drug abuse or dependence	19.1	18.9	.87
% With schizophrenia	0.6	0.8	.54
% With bipolar disorder	8.2	9.2	.18
% With depression	38.4	37.1	.25
% With anxiety disorder	11.6	12.9	.11
% With any psychiatric comorbidity	47.4	46.6	.52
No. of psychiatric diagnoses, mean (SD)	0.59 (0.70)	0.60 (0.73)	.51
Charlson Comorbidity Index, mean (SD)	0.33 (0.91)	0.34 (0.85)	.67
Chronic disease score, mean (SD)	2.58 (2.82)	2.59 (2.96)	.90
Pre–index date utilization, %			
Detoxification admission	23.5	22.2	.08
Alcoholism-related admission	18.8	19.3	.65
Nonalcoholism-related admission	18.4	19.5	.25
Alcoholism-related ED visit	21.2	21.1	.87
Psychiatrist visit	38.2	37.5	.50
Certified mental health counselor visit	0.5	0.7	.51
Drug copayment, mean (SD), $			
Extended-release injectable naltrexone hydrochloride	57 (56)	59 (60)	.92
Oral naltrexone	10 (6)	10 (6)	.69
Disulfiram	22 (10)	22 (10)	.001
Acamprosate calcium	34 (17)	35 (17)	.58
No. of psychiatrists per 1000 county-level population, mean (SD)	0.12 (0.12)	0.12 (0.12)	.14

ED indicates emergency department.

Table 2. Healthcare Utilization in the Groups Receiving Any vs No Alcoholism Medication

Variable	Receipt of Alcoholism Medication		
	Any (n = 2977)	None (n = 2977)	*P* Value
Inpatient services utilization			
% With detoxification admission	8.7	13.4	<.001
No. of detoxification days per 1000 patients, mean (SD)	706 (3422)	1163 (4552)	<.001
% With alcoholism-related admission	6.8	11.2	<.001
No. of alcoholism-related days per 1000 patients, mean (SD)	650 (3790)	1086 (5006)	<.001
% With nonalcoholism-related admission	11.4	11.6	.78
No. of nonalcoholism-related days per 1000 patients, mean (SD)	862 (4730)	967 (4703)	.39
Inpatient costs per 1000 patients, $			
Detoxification days	1,890,882	3,113,389	<.001
Alcoholism-related days	1,818,292	3,037,374	<.001
Alcoholism-related ED visits			
% With visit	8.3	10.3	.007
No. of visits per 1000 patients, mean (SD)	127 (553)	171 (657)	.005
Substance abuse and mental health visits			
% With substance abuse diagnosis	62.8	94.9	<.001
No. of substance abuse visits, mean (SD)	5.4 (8.6)	7.7 (9.0)	<.001
% With combined substance abuse and mental health diagnosis	80.8	97.3	<.001
No. of combined substance abuse and mental health visits, mean (SD)	9.0 (10.9)	10.5 (10.7)	<.001
Postperiod psychiatric comorbidity diagnoses			
% With schizophrenia	0.6	0.7	.64
% With bipolar disorder	9.6	9.0	.44
% With depression	36.8	32.5	<.001
% With anxiety disorder	11.4	9.8	.046
% With any psychiatric comorbidity	46.3	41.7	<.001
No. of psychiatric diagnoses, mean (SD)	0.58 (0.72)	0.52 (0.69)	<.001

ED indicates emergency department.

age of 45 years. During the preperiod, 19% had a drug abuse or dependence diagnosis, 8% to 9% had a bipolar disorder diagnosis, 37% to 38% had a depression diagnosis, and 12% to 13% had an anxiety disorder diagnosis. Preperiod alcoholism-related healthcare utilization was high, with 22% to 24% of patients having a detoxification admission, 19% having a hospital admission with a principal diagnosis of alcohol dependence, and 21% having an alcoholism-related ED visit in the 6 months before medication initiation.

Among the prematched sample, patients receiving any alcoholism medication were slightly older, more likely to be female, and more likely to live in areas with more college graduates, a higher median household income, and less poverty (**eAppendix B**). Patients prescribed any alcoholism medication were more likely to have a preperiod diagnosis of depression, anxiety disorder, or bipolar disorder. In the preperiod, the group receiving any alcoholism medication had higher percentages of patients with a detoxification admission, an alcoholism-related admission, or an alcoholism-related ED visit.

Table 2 gives utilization outcomes and postperiod psychiatric comorbidities in the 2 groups after propensity score matching. The group receiving no alcoholism medication had a higher percentage of patients with a detoxification admission after the index date (13% vs 9%, P <.001) and more inpatient detoxification days per 1000 patients (1163 vs 706, P <.001) than the group receiving any alcoholism medication. Inpatient detoxification days translated to costs of $1,890,822 per 1000 patients treated with any alcoholism medication and $3,113,389 per 1000 patients treated with no alcoholism medication.

The group receiving no alcoholism medication also had a higher percentage of patients with an inpatient admission for

a principal diagnosis of alcohol dependence (11% vs 7%, P <.001) and more alcoholism-related inpatient days (1086 vs 650, P <.001) (Table 2). Total charges for alcoholism-related inpatient days were estimated at $1,818,292 per 1000 patients treated with any alcoholism medication and $3,037,374 per 1000 patients treated with no alcoholism medication. There was no difference in the non-AUD inpatient admission rates. Finally, compared with groups receiving any alcoholism medication, the group receiving no alcoholism medication had a higher percentage of patients with alcoholism-related ED visits (10% vs 8%, P = .007) and had more alcoholism-related ED visits per 1000 patients (171 vs 127, P = .005).

The pattern of greater healthcare utilization among the group receiving no alcoholism medication was also true for outpatient visits. Compared with the group receiving any alcoholism medication, the group receiving no alcoholism medication was more likely to have an outpatient visit with a substance abuse diagnosis (95% vs 63%, P <.001) and had more substance abuse visits (7.7 vs 5.4, P <.001) (Table 2). The percentages of patients with schizophrenia, bipolar disorder, or anxiety disorder during the postperiod did not differ between the 2 study groups. The group receiving any alcoholism medication had a higher percentage of patients with a depression diagnosis than the group receiving no alcoholism medication (37% vs 33%, P <.001).

Comparisons Among 4 Alcoholism Medication Groups

Table 3 gives the characteristics of the 4 alcoholism medication groups after propensity score weighting. The characteristics were balanced across the groups. Differences among the 4 groups before weighting are given in eAppendix C.

Table 4 gives differences in outcomes after propensity score weighting across the 4 alcoholism medication groups. Patients receiving naltrexone XR had more time with filled prescriptions than patients receiving acamprosate (41% vs 34% of days covered in a 6-month period, P = .001).

Differences in percentages with detoxification admissions among the 4 alcoholism medication groups did not reach statistical significance at conventional levels. On average, the naltrexone XR group also had fewer inpatient detoxification days than the oral naltrexone group (P = .003) and the acamprosate group (P <.001) (Table 4). Fewer inpatient days translated to significantly lower inpatient costs per 1000 patients treated. Differences in percentages of patients with an alcoholism-related hospital admission did not reach statistical significance at conventional levels. On average, the naltrexone XR group had fewer alcoholism-related inpatient days than the disulfiram (P = .004) and acamprosate (P < .001) groups, which translated into lower inpatient costs per 1000 patients ($382,460 for naltrexone XR, $1,040,749 for disulfiram, and $1,214,881 for acamprosate).

A significantly higher percentage of patients receiving naltrexone XR (69%) had an outpatient visit for substance abuse treatment than patients receiving oral agents (38% for oral naltrexone, 40% for disulfiram, and 40% for acamprosate; P <.001) (Table 4). Similar results were found for the category of combined substance abuse and mental health visits. The difference in the mean number of outpatient substance abuse or mental health visits did not reach statistical significance.

There were no statistically significant differences among the 4 alcoholism medication groups in the percentages of patients diagnosed as having anxiety disorder, schizophrenia, bipolar disorder, depression, or any psychiatric diagnosis. Similarly, there were no significant differences in the numbers of psychiatric diagnoses.

DISCUSSION

In this retrospective claims analysis of matched commercially insured individuals, patients who received any alcoholism medication had fewer detoxification admissions, alcoholism-related inpatient care, alcoholism-related ED visits, and substance abuse outpatient visits in the 6 months following medication initiation than patients who received no alcoholism medication. Among the 4 groups of alcoholism medication users, naltrexone XR users were found to utilize more medication than acamprosate users. Furthermore, naltrexone XR use was associated with fewer inpatient detoxification days than oral naltrexone or acamprosate use and was associated with fewer inpatient days for a principal diagnosis of alcohol dependence than disulfiram or acamprosate use.

The data also reveal an inverse utilization pattern among 4 groups of alcoholism medication users relative to inpatient vs outpatient services. The naltrexone XR group had significantly less inpatient utilization, but significantly more patients in the naltrexone XR group had at least 1 outpatient substance abuse visit compared with patients receiving oral alcoholism agents. Higher outpatient services utilization may be an indication of better engagement, which may have contributed to lower inpatient services utilization. Notably, patients who used no alcoholism medication had greater outpatient services utilization than patients who used any alcoholism medication; however, there was no corresponding decline in inpatient services utilization. This finding suggests that engagement in outpatient treatment should be associated with better utilization outcomes, but perhaps only if that treatment is comprehensive in addressing both psychosocial and biologic aspects of alcohol dependence. Indeed, this conclusion is consistent with guidelines published by the National Institute

■ **Table 3.** Characteristics of Inverse Probability–Weighted Patients Receiving Extended-Release Injectable Naltrexone Hydrochloride (Naltrexone XR), Oral Naltrexone, Disulfiram, or Acamprosate Calcium

Variable	Naltrexone XR (n = 295)	Oral Naltrexone (n = 2064)	Disulfiram (n = 2076)	Acamprosate (n = 5068)	*P* Value: Naltrexone XR vs Oral Naltrexone	*P* Value: Naltrexone XR vs Disulfiram	*P* Value: Naltrexone XR vs Acamprosate
Male sex, %	53.3	59.3	58.0	58.5	.12	.22	.16
Age group, y, %							
18-34	15.7	15.5	16.2	16.2	.93	.86	.85
35-44	23.0	25.4	24.3	25.1	.46	.68	.49
45-54	40.6	36.8	36.5	36.6	.34	.29	.29
55-64	20.8	22.3	23.0	22.1	.60	.46	.64
Geographic region, %							
Northeast	13.8	11.5	11.7	11.5	.29	.36	.29
North central	35.2	32.2	32.0	32.4	.43	.39	.45
South	30.1	34.0	33.8	33.7	.22	.25	.24
West	20.1	21.4	21.8	21.6	.70	.63	.66
Relationship to employee, %							
Self	57.4	60.5	60.1	60.4	.41	.48	.42
Spouse or partner	37.5	33.8	34.2	33.8	.32	.38	.31
Child or dependent	5.2	5.7	5.7	5.9	.77	.76	.71
Neighborhood characteristics							
Median household income, mean (SD), $	53,061 (110,469)	51,738 (37,883)	51,631 (39,480)	51,719 (24,714)	.35	.32	.33
% Below poverty level	9.0	9.0	9.1	9.0	.93	.89	>.99
% African American	8.1	8.9	9.0	8.9	.41	.33	.32
% College graduate	30.1	28.1	28.3	28.1	.11	.14	.10
Preperiod psychiatric comorbidity diagnosis							
% With alcohol use disorder	39.3	44.4	43.1	42.5	.15	.28	.34
% With drug abuse or dependence	12.5	12.8	13.2	13.2	.87	.74	.74
% With schizophrenia	0.5	0.9	0.7	0.6	.41	.67	.86
% With bipolar disorder	11.5	10.2	9.6	8.8	.54	.36	.15
% With depression	35.2	34.7	37.0	35.0	.90	.62	.96
% With anxiety disorder	9.6	10.2	9.9	11.0	.78	.88	.50
% With any psychiatric comorbidity	46.7	44.9	46.1	45.2	.63	.88	.68
No. of psychiatric diagnoses, mean (SD)	0.57 (0.79)	0.56 (0.76)	0.57 (0.84)	0.55 (0.71)	.88	.94	.75
Charlson Comorbidity Index, mean (SD)	0.28 (4.75)	0.24 (1.76)	0.26 (1.75)	0.26 (1.08)	.53	.73	.70
Chronic disease score, mean (SD)	2.57 (14.51)	2.69 (6.12)	2.78 (6.28)	2.72 (3.90)	.50	.25	.39
Pre–index date utilization, %							
Detoxification admission	15.1	16.9	17.9	17.1	.45	.26	.36
Alcoholism-related admission	7.6	8.1	7.7	8.8	.75	.95	.44
Nonalcoholism-related admission	15.2	12.6	13.8	12.4	.38	.67	.34
Alcoholism-related ED visit	9.0	9.2	10.3	9.8	.92	.48	.64
Psychiatrist visit	36.9	37.3	31.6	35.0	.90	.14	.59
Certified mental health counselor visit	0.4	0.5	0.6	0.6	.86	.71	.74
Drug copayment, mean (SD), $							
Naltrexone XR	59 (294)	63 (126)	58 (123)	63 (81)	.39	.89	.35
Oral naltrexone	23 (56)	22 (23)	22 (21)	23 (15)	.29	.51	.38
Disulfiram	33 (94)	35 (38)	36 (37)	35 (24)	.56	.27	.93
Acamprosate	10 (31)	10 (16)	10 (11)	10 (9)	.21	.14	.31
No. of psychiatrists per 1000 county-level population, mean (SD)	0.13 (0.81)	0.12 (0.27)	0.12 (0.28)	0.12 (0.17)	.38	.38	.35

ED indicates emergency department.

Table 4. Outcomes of Patients Receiving Extended-Release Injectable Naltrexone Hydrochloride (Naltrexone XR), Oral Naltrexone, Disulfiram, or Acamprosate Calcium

Variable	Naltrexone XR Value (n = 295)	Oral Naltrexone (n = 2064)		Disulfiram (n = 2076)		Acamprosate (n = 5068)	
		Value	*P* Value	Value	*P* Value	Value	*P* Value
% Of 180 days covered, mean (SD)	41 (34)	37 (61)	.09	37 (58)	.09	34 (34)	.001
Inpatient services utilization							
% With detoxification admission	4.1	5.7	.25	5.8	.24	6.5	.09
No. of detoxification days per 1000 patients, mean (SD)	224 (8021)	552 (6723)	.003	403 (4795)	.049	525 (4153)	<.001
% With alcoholism-related admission	2.3	3.1	.38	4.4	.07	4.5	.04
No. of alcoholism-related days per 1000 patients, mean (SD)	137 (7022)	229 (6427)	.24	372 (5605)	.004	435 (4345)	<.001
% With nonalcoholism-related admission	9.4	9.4	.99	9.7	.91	9.8	.87
No. of nonalcoholism-related days per 1000 patients, mean (SD)	869 (31,004)	589 (6866)	.33	697 (8693)	.57	767 (9178)	.73
Inpatient costs per 1000 patients, $							
Detoxification days	600,146	1,479,416	<.01	1,079,371	.05	1,404,996	<.01
Alcoholism-related days	382,460	641,395	.24	1,040,749	<.01	1,215,881	<.01
Alcoholism-related ED visits							
% With visit	5.7	4.4	.40	5.5	.91	5.7	>.99
No. of visits per 1000 patients, mean (SD)	65 (1593)	57 (648)	.71	82 (879)	.45	85 (614)	.29
Substance abuse and mental health outpatient visits							
% With substance abuse diagnosis	68.6	38.0	<.001	40.2	<.001	40.1	<.001
No. of substance abuse visits, mean (SD)	3.81 (34.98)	2.98 (13.89)	.045	3.2 (16.33)	.17	3.09 (9.31)	.07
% With combined substance abuse and mental health diagnosis	85.1	68.6	<.001	66.3	<.001	69.3	<.001
No. of combined substance abuse and mental health visits, mean (SD)	7.21 (50.58)	6.69 (20.58)	.41	6.68 (21.35)	.41	6.63 (12.96)	.35
Postperiod psychiatric comorbidity diagnoses							
% With schizophrenia	1.1	0.7	.44	0.6	.34	0.6	.30
% With bipolar disorder	10.4	11.4	.66	10.3	.98	10.3	.95
% With depression	32.2	35.4	.39	32.6	.92	36.1	.28
% With anxiety disorder	6.0	10.1	.04	10.3	.03	11.2	.01
% With any psychiatric comorbidity	41.8	45.9	.29	43.9	.59	46.9	.17
No. of psychiatric diagnoses, mean (SD)	0.5 (0.76)	0.58 (0.78)	.10	0.54 (0.80)	.38	0.58 (0.72)	.06

ED indicates emergency department.

on Alcohol Abuse and Alcoholism stating that psychosocial approaches and medication use are complementary and "share the same goals while addressing different aspects of alcohol dependence: neurobiological, psychological, and social."[4]

This study must be understood in light of its limitations. First, the observed associations may not be causal. Without randomization, there may be unmeasured confounding factors such as differential motivation and illness severity that underlie the observed differences in utilization. This risk may have been mitigated by baseline propensity score matching and weighting for relevant demographic, baseline clinical, and utilization variables. Furthermore, the results derive from a range of practices, settings, and provider types in community settings, which enhances external validity. Second, the study examined only commercial claims; therefore, the results may not generalize to other populations such as Medicaid beneficiaries. However, in parallel analyses among a limited number of Medicaid patients, results were consistent with the findings

presented herein, providing further support for their external validity. Third, study outcomes were utilization measures that, while important, did not include alcohol consumption patterns. However, intensive healthcare services utilization (eg, the number of subsequent inpatient detoxification days) may be a reasonable proxy for drinking behavior. Fourth, because of the recent introduction of naltrexone XR, the sample of 295 users of naltrexone XR was small, which may have limited the statistical power, and should be expanded in future analyses. Fifth, the inclusion criteria required continuous enrollment for 1 year, and individuals with continuous enrollment may have differed from those without continuous enrollment (eg, because of job loss) in severity, adherence, and outcomes. Sixth, comparisons across products did not attempt to control for the extent to which patients filled an "adequate" course of the medication, as the study intent was to focus on the effect of outcomes of the "usual" treatment patterns; however, this would be a useful follow-up study. Seventh, adherence was measured according to filled paid claims, and while naltrexone XR is administered by a health professional and persists over 1 month, patients receiving oral agents may not have taken them as prescribed.

These findings are clinically significant and address the significant gap in information on the effects of alcoholism medications in clinical practice. Despite general research that has shown benefits of these medications in the treatment of alcohol dependence and the recommendation by the National Institute on Alcohol Abuse and Alcoholism[4] that providers should consider the use of approved medications for the treatment of all patients with alcohol dependence, it is estimated that more than 90% of patients diagnosed as having alcohol dependence do not receive such pharmacotherapy.[5] In this study, we found a consistent pattern of better outcomes associated with pharmacotherapy than with no pharmacotherapy. Similarly, naltrexone XR use was associated with better outcomes than the use of oral alcoholism medications in many comparisons. Differences are clinically and economically meaningful. For example, when inpatient detoxification days are converted to hospital charges using the mean daily charges reported by US insurers (based on Healthcare Cost and Utilization Project National Inpatient Sample data for 2007 from the US Agency for Healthcare Research and Quality [http://hcupnet.ahrq.gov/]), naltrexone XR use was associated with significantly lower detoxification costs ($0.60 million per 1000 patients over 6 months) than oral naltrexone use ($1.48 million, P <.01), disulfiram ($1.08 million, P = .05), or acamprosate ($1.40 million, P <.01) (Table 4).

Prior studies[6,8-10] of oral naltrexone have shown that most patients do not persist through a clinically relevant course of treatment, and nonpersistence has been associated with significantly more intensive healthcare services utilization.[9] In the present study, the group receiving naltrexone XR had greater medication utilization and lower inpatient services utilization and costs than the groups receiving oral alcoholism medications. These findings may be attributable to the administration of naltrexone XR formulation on a monthly basis rather than a daily basis. The findings from this study have important implications for alcohol dependence pharmacotherapy and provide support for the use of FDA-approved medications, particularly naltrexone XR, in clinical settings. Additional comparative research on alcohol dependence pharmacotherapy using larger samples and longer durations of treatment is needed to enhance the care of this undertreated patient population.

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