COST AND UTILIZATION OF EXTENDED RELEASE NALTREXONE FOR ALCOHOL USE DISORDERS

By

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CERTIFICATE OF APPROVAL

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ABSTRACT

Objective: Insurance claims data from Aetna Behavioral Health were collected to assess health care costs, utilization, and persistence with treatment among Aetna beneficiaries receiving XR-NTX for AUDs compared to those receiving (1) disulfiram, (2) oral NTX, (3) acamprosate, and (4) psychosocial therapy only. *Methods*: Aetna extracted patient-level data from their national claims and utilization database for Aetna beneficiaries receiving XR-NTX (*n* = 211), disulfiram (*n = 1,043*), oral NTX (*n = 1,408*), acamprosate (*n = 2,479*), or psychosocial therapy only (*n = 6,374*) for AUDs from 1/1/07 – 12/31/08. Survival analysis compared persistence with XR-NTX vs. oral pharmacotherapies over a six month period. Difference-in-differences analysis compared health care costs and utilization among those receiving XR-NTX vs. oral pharmacotherapies and psychosocial therapy only. Multivariate analyses controlled for demographics. Stratification over physical and mental health comorbidities accounted for interactions. *Results*: Patients taking acamprosate and disulfiram were more likely to discontinue treatment during the six-month follow-up period than patients taking XR-NTX or oral NTX, and oral NTX patients were more likely to discontinue treatment than XR-NTX patients. Outpatient behavioral health utilization increased with treatment in all study groups. Non-pharmacy health care costs and utilization of inpatient and emergency services decreased in the XR-NTX group relative to other study groups, especially in patients with physical and mental health comorbidities. *Conclusions*: Naltrexone patients persisted with treatment longer than acamprosate and disulfiram patients, and XR-NTX longer than oral NTX. XR-NTX patients decreased non-pharmacy spending and utilization to a greater extent than comparison groups, and all groups increased outpatient behavioral health utilization. These trends were particularly strong in patients with comorbidities.

I. INTRODUCTION

BACKGROUND

Burden of Alcohol Use and Misuse in the United States. The estimated economic cost to society of alcohol abuse increased from 148 million dollars in 1992 to 184 million dollars in 1998, after adjusting for changes in the population, alcohol use disorder (AUD) diagnoses, general prices, and wages.[1] Surveillance data from the National Institute of Alcohol Abuse and Alcoholism reported that per capita alcohol consumption has risen each year since 1998.[2] Between 2000 and 2008, the Substance Abuse and Mental Health Services Administration's (SAMHSA) Office of Applied Studies (OAS)reports that total use, binge drinking, and heavy use have risen among Americans over the age of twelve.[3,4] In 2000, alcohol was identified as the third leading cause of preventable deaths in the United States, behind only tobacco and poor diet/physical inactivity.[5] Rising trends in alcohol use and misuse over the past decade may exacerbate the already significant economic and health consequences of alcoholism.

Pharmacotherapy for Alcohol Use Disorders. The burden of alcohol use and misuse appears to have worsened over the past two decades despite the development of medications that target alcohol dependence. In addition to disulfiram, an alcohol-sensitizing drug that was approved by the U.S. Food and Drug Administration in 1949, three other medications have been approved for the treatment of alcohol dependence in the past 15 years: oral naltrexone (oral NTX) in 1994; acamprosate in 2004; and injectable, extended release naltrexone (XR-NTX) in 2006. Although prevailing treatment models for AUDs rely on psychosocial therapy, there is evidence that these recently developed medications are efficacious adjuncts for traditional treatment modalities.[6]

Disulfiram.

Disulfiram irreversibly binds to the enzyme aldehyde dehydrogenase such that alcohol consumption and subsequent metabolism leads to an accumulation of acetaldehyde, which produces unpleasant deterrent effects that can be severe.[7] The FDA approved disulfiram prior to the implementation of scrupulous efficacy standards, and subsequent studies have demonstrated modest efficacy in reducing drinking frequency without improving abstinence.[8] Poor adherence limits its effectiveness[9], but behavioral interventions such as direct supervision of treatment can improve adherence and outcomes.[10]

Oral Naltrexone.

Oral NTX is a competitive antagonist of the mu opioid receptor that decreases cravings related to the positive reinforcing effects of alcohol.[11] Several meta-analyses conducted after its approval in 1994 have found that oral NTX is consistently associated with moderate reduction in alcohol consumption, and inconsistently associated with increased abstinence.[12-15] The COMBINE study, which is the largest randomized controlled trial of alcohol pharmacotherapy to date, compared the efficacy of oral NTX, acamprosate, behavioral therapy, and medical management. When combined with behavioral therapy or medical management, oral NTX increased abstinent days and reduced the risk of heavy drinking.[16]

In practice, however, the effectiveness of oral NTX has been hindered by poor adherence.[17,18] Volpicelli et al found that subjects must take at least 85% of their daily doses of oral NTX to experience therapeutic response[19], which may be related to low trough levels.[20] Conversely, high peak levels are considered to be responsible for adverse events that are associated with nonadherence.[21]

Extended Release Naltrexone.

To address the pharmacokinetic problems of oral NTX, injectable extended-release (XR) preparations were developed and approved in 2006.[20] There have been few studies addressing the efficacy of XR-NTX. One multicenter, randomized controlled trial found that XR-NTX was associated with greater time to first drink, fewer drinking days, and greater rate of abstinence compared to placebo over a 12 week period.[22] Garbutt et al conducted another multicenter, randomized controlled trial and reported that subjects receiving XR-NTX had fewer heavy drinking days compared to placebo over a six month period.[23] A secondary analysis of the Garbutt et al data restricted to only those subjects who were voluntarily abstinent prior to the study, finding that those taking XR-NTX experienced longer time to first drink and greater abstinence rates compared to those taking placebo.[24]

Acamprosate.

Finally, acamprosate increases γ-aminobutyric acid (GABA) signaling and exerts complex effects on glutamate pathways, but its precise mechanism of action remains unclear.[25] It has been available in Europe since 1989, and several European studies have demonstrated the efficacy of acamprosate in the treatment of alcohol dependence, primarily for outcomes related to abstinence.[12,14,26,27] These European studies formed the basis upon which acamprosate was approved in the United States in 2005. However, the American COMBINE study failed to find a difference between acamprosate and placebo groups.[16] Disagreement between American and European studies of acamprosate may reflect differences in study design and subjects.[28]

Alcohol Pharmacotherapy Prescribing Trends. Despite evidence of efficacy, the trends in utilization of pharmacotherapies for AUDs have been underwhelming since the approval of oral NTX in 1994. Ducharme et al examined utilization trends among 252 private sector treatment programs between 1995 and 2004, the year before acamprosate was approved, and found that

the proportion of treatment programs reporting disulfiram use fell from 52% to 36%, while oral NTX use dropped from 49% to 42%.[29] Over the study period, the researchers found that approximately one third of the programs permanently adopted oral NTX, one third used it occasionally, and one third never used it. They also examined treatment program characteristics that were associated with disulfiram and oral NTX adoption. Accreditation, focusing on dual-diagnosis, having physician(s) on staff, and having a high percentage of revenue from insurance were associated with use of disulfiram and oral NTX.

A more recent study found similar prescription patterns between 2003 and 2007, using data from the IMS National Prescription Audit Plus database of retail pharmacy transactions.[30] Mark et al reported that overall alcohol pharmacotherapy prescriptions increased at an average annual growth rate of 12.9% per year, from 393,000 in 2003 to 720,000 in 2007. The increase was primarily driven by acamprosate prescriptions, which increased at an average rate of 10.6% per year since its introduction in 2005. Between 2003 and 2007, disulfiram prescriptions fell at an average rate of 3% per year, whereas oral NTX prescriptions increased by 3.6% per year. Over the same period, the proportion of alcohol pharmacotherapy prescriptions for which disulfiram accounts fell from 53% to 25%, and oral NTX dropped from 47% to 31%. Acamprosate replaced oral NTX and disulfiram, accounting for 43% of alcohol pharmacotherapy prescriptions in 2007. XR-NTX accounted for 2% of alcohol pharmacotherapy prescriptions in 2007, the year after its approval.

Harris and colleagues investigated alcohol pharmacotherapy prescribing trends in the Veterans Health Administration during 2006 and 2007.[31] They found that only 2.8% of VA subjects with alcohol use disorders received any alcohol pharmacotherapy in 2006, and the proportion remained stable at 3.0% in 2007. Oral NTX and disulfiram comprised the majority of alcohol pharmacotherapy prescriptions, in large part because acamprosate is not on formulary

in the VA (neither is XR-NTX). XR-NTX accounted for 0.0% and 0.8% of VA alcohol pharmacotherapy prescriptions in 2006 and 2007, respectively, compared to 48.6% and 53.2% for oral NTX, 41.4% and 36.3% for disulfiram, and 17.7% and 18.7% for acamprosate.

Barriers to Adoption of Pharmacotherapy for Alcohol Use Disorders. Historically, alcohol abuse and dependence treatment has been conducted in outpatient, group-based treatment programs. These programs rely primarily on non-physician personnel, and have generally conformed to the 12-step philosophy, focusing on total abstinence as the only acceptable treatment goal. These organizations face several inherent barriers to the adoption of medications that reduce the amount of drinking, including treatment philosophy and lack of organizational support, staff composition, staff awareness and attitudes, and price and reimbursement. Authors have argued that the reason for the disproportionate adoption of acamprosate relative to oral NTX and disulfiram is that acamprosate better aligns with traditional philosophies of abstinence promotion.[29,30] Acamprosate has also benefited from more forceful marketing.[30] Adoption of acamprosate has occurred in spite of the results of the COMBINE study, which supported the efficacy of oral NTX but not acamprosate.[16] The alcohol addiction treatment field has been slow to adopt evidence-based practices including pharmacotherapy.[32]

Organizational Barriers.

Over the past ten years, a handful of studies have examined organizational factors that influence the adoption of alcohol pharmacotherapy in alcohol treatment programs. One study found that physicians and counselors who worked for organizations that actively promoted oral NTX were more likely to prescribe or recommend it.[33] Another study reported that larger outpatient treatment programs were more likely to prescribe oral NTX than smaller programs,

whereas treatment programs with a primary corporate mission of substance abuse treatment were less likely to prescribe oral NTX than programs with a mission related to general health, mental health, or multiservice care.[34] The researchers contend that programs with a primary mission of treating substance abuse may lack necessary training, staff that can prescribe medication, or a philosophical approach compatible with pharmacotherapy for AUDs.

Provider Characteristics Barriers.

Provider characteristics have also been identified as important determinants of NTX adoption. One study found that physicians with board certification in psychiatry have adopted oral NTX more quickly than other physicians.[35] Similarly, physicians who prescribed oral NTX reported having been exposed to more information on NTX than non-prescribers, and a higher proportion of prescribers could summarize research evidence regarding NTX. Another study showed that the proportion of prescriptions coming from family, internal, and general medicine physicians was lower for NTX than acamprosate or disulfiram.[30] Moreover, physicians in recovery were less likely to prescribe oral NTX.[33] The researchers propose that these physicians went through traditional, 12-step programs and had personal investment in the traditional treatment model and its focus on abstinence.

Provider Attitudes Barriers.

Evidence exists to support the idea that provider attitudes and awareness are influential factors in the adoption of pharmacotherapy for AUDs. One study documented self-reported barriers to oral NTX adoption among physicians.[35] The most common perceived barriers were: patients refused to take or adhere to treatment (23%); patients could not afford the medications (21%); patients were not in a formal treatment program (15%); the effect of the medication was small compared to side effects (12%); and concerns about side effects (10%). Another study identified the perception among physicians that addiction pharmacotherapies are more difficult to

prescribe or more complex than other medications.[36] Among counselors, education level was positively correlated with NTX use.[34] Counselor education was also negatively correlated with staff being in recovery.

Financial Barriers.

Finally, reimbursement and financing issues have been identified as important determinants of NTX adoption. One study found that oral NTX-prescribing physicians tended to treat a relatively high proportion of subjects with private insurance or Medicare, and a relatively low proportion of subjects with block grant coverage, Medicaid, or no insurance.[35] Another study described similar findings, except that they found a positive association between Medicaid subjects and oral NTX prescription.[33] This discrepancy suggests that Medicaid reimbursement differs across states despite the fact that oral NTX was covered by Medicaid at the time of both studies. A third study reported that receiving revenues from managed care plans was positively correlated with counselor education and NTX adoption.[34]

SIGNIFICANCE

This study conducts a secondary analysis of Aetna insurance claims data to assess health care costs and utilization among Aetna beneficiaries taking XR-NTX for AUDs in comparison to those taking oral alcohol pharmacotherapies including disulfiram, acamprosate, and oral NTX. Poor patient adherence is a well-documented problem among oral alcohol pharmacotherapies for reasons that include side effects, impatience while waiting for the medication to work, and lack of understanding of the need for consistent dosing.[37] Recent studies have documented poor

persistence* with oral NTX.[18,38,39] XR-NTX was developed to address these issues with improved pharmacokinetic properties and a monthly dosing regimen.[20] Therefore, this study assesses persistence with treatment among Aetna beneficiaries taking XR-NTX for AUDs in comparison to those taking oral pharmacotherapies, hypothesizing that persistence is greater among patients taking XR-NTX. The study also hypothesizes that utilization of outpatient addiction treatment increases more among patients taking XR-NTX than patients taking oral pharmacotherapies, reflecting better adherence among the XR-NTX group. The study further hypothesizes that non-pharmacy health care costs and utilization decrease among patients taking XR-NTX relative to patients taking oral pharmacotherapies.

This study also evaluates non-pharmacy health care costs and utilization among Aetna beneficiaries taking XR-NTX-assisted treatment for AUDs in comparison to those receiving psychosocial therapy only. One previous study has compared health care costs and utilization between patients who received oral NTX vs. psychosocial therapy only, reporting that the oral NTX group decreased utilization and spending relative to the psychosocial therapy only group.[40] Given the efficacy of NTX[25] and the hypothesized adherence advantage of XR-NTX over oral NTX, this study hypothesizes that health care costs and utilization decrease for those taking XR-NTX-assisted treatment compared to those receiving psychosocial therapy only.

Finally, the study examines health care spending and utilization in subpopulations of Aetna beneficiaries with physical and mental health comorbidities. The study hypothesizes that spending and utilization decreases with XR-NTX relative to oral pharmacotherapies and psychosocial therapy only are particularly pronounced among patients with comorbidities.

* Persistence refers to the consistency with which patients fill prescriptions for their medications. This is opposed to adherence, which refers to the extent to which patient behavior corresponds to medical advice.

Weisner and colleagues have demonstrated that only integration of primary care and substance abuse treatment was only cost-effective for individuals with substance abuse-related medical conditions.[41] It may follow that alcohol medications affect costs and utilization within an integrated health plan differently for those with vs. without comorbid physical and mental health diagnoses.

Demonstrating that alcohol pharmacotherapies are associated with spending reductions may motivate insurance companies, Medicare, and Medicaid to provide better and more reliable coverage for medication-assisted treatment of AUDs. It may also motivate substance abuse treatment programs to offer organizational support for alcohol pharmacotherapies and promote staff education, which are critical factors in facilitating adoption.[33-35]

II. MATERIALS AND METHODS

STUDY DESIGN

***Study Population*.** For this historical cohort study, the population of interest included all Aetna Behavioral Health (ABH) members enrolled in the Alcohol Disorder Disease Management Program (AD-DMP) who began pharmacologic or psychosocial treatment for alcohol use disorders (AUDs) between 1/1/07 and 12/31/08. Patient-level data on allowed behavioral, physical, and prescription drug claims and utilization were stored in an integrated national database. Claims and utilization data were used to identify patients for enrollment in the AD-DMP program whose treatment patterns are consistent with AUDs.

Aetna Behavioral Health and Disease Management Programs. Aetna Behavioral Health coordinates the management of physical care with services for alcohol, drug and mental health problems using an integrated database. Individuals with both physical and behavioral health disorders are eligible for enrollment in Aetna's DMP. Behavioral health counselors and nurses work with primary care providers to coordinate care, implement treatment plans, and support patient adherence. One part of the DMP is to facilitate access to medication-assisted treatment.

The DMP uses concurrent review of claims data to identify individuals receiving treatment for alcohol and drug disorders. Alcohol and drug dependent individuals with Aetna's Medical, Behavioral Health and Pharmacy benefits are eligible to participate in the Medication Support Program, which coordinates access to physician services for prescriptions and to ongoing addiction treatment for counseling. Clinicians within ABH act as resource managers.

***Selection Criteria*.** Selection criteria for enrollment in the Aetna Behavioral Health Alcohol Disorder Disease Management Program were as follows:

Inclusion	Exclusion
Aetna beneficiaries	Did not receive health insurance from Aetna
Members were "flagged" with AUD if claims data reveals: 1. Inpatient care for detoxification, including medical treatment and referral services for alcohol abuse or addiction. 2. Inpatient medical, nursing, counseling and therapeutic rehabilitation services for treatment of alcohol abuse or dependency in an appropriately licensed facility. 3. Outpatient visits for detoxification, including diagnosis, medical treatment and medical referral services. 4. Outpatient visits for diagnostic, medical or therapeutic rehabilitation services for alcohol abuse.	Claims review did not identify AUD
Eligible member agreed to participate in AD-DMP	Eligible member declined to participate

Inpatient admissions were considered to constitute AUD treatment if the primary diagnosis at discharge and the majority of all primary diagnoses in the inpatient record were alcohol abuse diagnoses. Outpatient visits were identified as AUD treatment if the primary diagnosis was for AUD, if there was an indication that a procedure to treat AUD was performed, or if Aetna's specific coding identified a service as related to an AUD. Selection criteria for the proposed secondary analysis of Aetna members eligible for AD-DMP enrollment were as follows:

Group	Inclusion	Exclusion
All Patients	Aetna members who were eligible for enrollment in the AD-DMP	Aetna members who did not qualify for the AD-DMP
	Patient was continuously enrolled with Aetna for at least six months before and after the index date	Patient was not continuously enrolled with Aetna throughout the specified time period
	Patient did not have any single claims in excess of $25,000	Patient had at least one single claim in excess of $25,000
All Medication-assisted Groups	Patient filled at least one prescription for XR-NTX, oral NTX, acamprosate, or disulfiram from 1/1/07 – 12/31/08	Patient did not take medication for AUD within the study period
	Patient did not take any medications for AUDs in the three months prior to index date	Patient filled prescriptions for AUD medications in the three months prior to index date
	Patient received only one medication for AUDs during the six months after index date	Patient filled prescriptions for multiple AUD drugs during the six months after index date

Group	Inclusion	Exclusion
Psychosocial Therapy Only Group	Patient initiated outpatient psychosocial therapy for AUD during 1/1/07 – 12/31/08	Patient had no allowed claims for psychosocial therapy for AUD in Aetna database
	Patient did not take any AUD medication previously	Patient took an AUD medication previously

The index date for patients receiving medications for AUDs was defined as the date on which they filled their first prescription. For the psychosocial therapy only group, the index date was defined as the date of service for a claim that included a Current Procedural Code (CPT) of 90801 and an AUD diagnosis.

The XR-NTX study group consisted of Aetna beneficiaries whose index date for XR-NTX treatment occurred between 1/1/07 and 12/31/08, and who met inclusion criteria required of all patients as well as patients in medication-assisted groups. These patients were identified as receiving XR-NTX by the Generic Product Identifier (GPI) code 93400030001920. There were four comparison groups: (1) oral NTX; (2) acamprosate; (3) disulfiram; and (4) psychosocial therapy only. The oral NTX comparison group consisted of Aetna beneficiaries whose index date for oral NTX treatment fell between 1/1/07 and 12/31/08, and who met inclusion criteria required of all patients and patients in medication-assisted groups. These patients were identified as receiving oral NTX by the GPI code 93400030100305. The acamprosate comparison group consisted of Aetna beneficiaries whose index date for acamprosate treatment fell between 1/1/07 and 12/31/08, and who met inclusion criteria required of all patients as well as patients in medication-assisted groups. These patients were identified as receiving acamprosate by the GPI code 62802010200620. The disulfiram comparison group consisted of Aetna beneficiaries whose index date for disulfiram treatment fell between 1/1/07 and 12/31/08, and who met inclusion criteria required of all patients as well as patients in medication-assisted groups. These patients were identified as receiving disulfiram by the GPI codes

96485857002900 or 62802040000325. Finally, the psychosocial therapy only study group consisted of Aetna beneficiaries whose index date for psychosocial therapy for AUDs occurred between 1/1/07 and 12/31/08, and who met inclusion criteria required of all patients as well as patients in the psychosocial therapy only group. Psychosocial therapy consisted of any outpatient psychiatrist or therapist visits for which insurance claims were filed. It did not include free services such as Alcoholics Anonymous.

Patient Recruitment. Patients were not directly recruited to participate in this secondary analysis. Aetna used pre-authorized claims review to identify members eligible for the AD-DMP. Eligible members who met selection criteria for the secondary analysis were included in the study. Aetna fully de-identified the participating patients' claims data before supplying them for secondary analysis.

Measurement and Data Collection. Aetna extracted patient-level data from the ABH claims and utilization database for all members filling their first prescriptions for XR-NTX (*n = 211*), oral NTX (*n = 1,408*), acamprosate (*n = 2,479*), or disulfiram (*n = 1,043*) for AUDs between 1/1/07 – 12/31/08. They also extracted data for a random sample of members beginning outpatient psychosocial therapy (*n = 6,374*) for AUDs between 1/1/07 – 12/31/08. Data came from an administrative claims database with integrated and linkable information on members, employers, medical and pharmacy claims, and benefit and plan design. Claims were available for extraction 12 to 16 weeks after the patient-provider encounter. For all groups, claim collection was limited to the period between 6/1/06 – 6/30/09.

VARIABLES

Outcome Variables. The secondary analysis assessed differences in health care costs and utilization between Aetna beneficiaries receiving XR-NTX vs. oral medications or psychosocial therapy only for AUDs. Primary outcome variables represented (1) persistence with medication, (2) health care spending, and (3) health care utilization. All spending and utilization outcome variables were aggregated over the six months before vs. after the index date.

The variable representing persistence measured the number of consecutive days for which each patient had alcohol pharmacotherapy in his or her possession, beginning with the index date. Patients were considered to be in possession of alcohol pharmacotherapy from the date they filled a prescription until the date it expired. Non-persistence was defined as the first time after the index date that patients went more than ten consecutive days without medication in their possession. Therefore, patients were given ten days after each prescription expired to fill the next without being considered non-persistent. The ten day interval was selected empirically, as the data indicated that patients who refilled prescriptions within ten days tended to continue filling prescriptions regularly, whereas patients who took longer than ten days to refill prescriptions tended to discontinue treatment. Since patients were followed for six months (180 days) after the index date, the maximum length of time a patient could be persistent was 180 days. Data were censored beyond 180 days.

Health care spending measured the total non-pharmacy health care costs recorded in the Aetna claims database during the 6 month pre- and post-index periods, including out-of-pocket and health plan expenses. Subanalyses considered the subsets of costs attributable to (a) behavioral health care, and (b) physical health care. Pharmacy claims were not included in the health care spending variables.

Measurements of health care utilization encompassed the number of inpatient admissions (count variable), days spent in inpatient treatment (count variable), the number of behavioral health outpatient visits (count variable), and the number of emergency department visits (count variable). Inpatient admissions and days in treatment were divided into components attributable to physical vs. behavioral health care. Outpatient behavioral health visits were divided into psychosocial therapy visits (psychiatrist and therapist visits) and outpatient visits to a hospital/inpatient facility (intensive outpatient treatment, partial hospitalization). Outpatient behavioral health visits to hospitals/facilities did not include visits that culminated in full inpatient admissions.

Outcomes	**Outcome Variable Constructs**	**Units**	**Type of Variable**
Health Care Spending	Total Spending *Behavioral Health Spending* *Physical Health Spending*	Dollars	Continuous
Health Care Utilization	Inpatient Admissions *Behavioral Admissions* *Physical Health Admissions*	Number of Admissions	Count
	Inpatient Days *Behavioral Health Days* *Physical Health Days*	Number of Days in Inpatient Treatment	
	Behavioral Health Outpatient Visits *Psychosocial Therapy Visits* *Hospital/Facility Visits*	Number of Visits	
	Emergency Department Visits		
Persistence	Persistence with Pharmacotherapy	Number of consecutive days in possession of drug	Continuous

Aetna used internal algorithms to classify claims as physical or behavioral health. Claims identified as pharmacy expenses were not included in the data set. Inpatient admissions were identified as behavioral health care admissions if the primary diagnosis at discharge and the majority of all primary diagnoses in the inpatient record were mental health or substance abuse diagnoses. Outpatient visits were identified as behavioral health treatment if the primary diagnosis was for mental health or substance abuse, if there was an indication that a behavioral

health procedure was performed, or if Aetna's specific coding identified a service as related to behavioral health. Utilization that was not defined as behavioral health was classified as physical health.

Definition of Behavioral Health Utilization and Spending	
Behavioral Health Inpatient Admissions • 1^{o} diagnosis at discharge was behavioral health, AND • The majority of all 1^{o} diagnoses in the inpatient record were behavioral health	Behavioral Health Outpatient Visits • 1^{o} diagnosis was behavioral health, OR • There was indication that a behavioral health procedure was performed, OR • Aetna's specific coding identified a service related to behavioral health

Predictor Variables. The primary predictors of interest represented (1) time relative to initiation of AUD treatment, and (2) study (medication) group. There were five distinct study groups: (a) XR-NTX, (b) oral NTX, (c) acamprosate, (d) disulfiram, and (e) control (psychosocial therapy only). Both the time and medication variables were represented by dummy variables. The dichotomous time variable was divided into pre- vs. post-intervention periods. It equaled zero for the 6 month pre-intervention period, and 1 for the 6 month post-intervention period. Study group was a five-level categorical variable, represented by four dummy variables. XR-NTX served as the reference group, and each of the other four comparison groups had a dichotomous dummy variable that had the value 1 for patients taking that medication and 0 otherwise. XR-NTX patients were assigned zeroes for all study group dummies.

Predictor	Predictor Variable	Type	Values
Time Relative to Treatment Start Date • 6 month pre-treatment period • 6 month post-treatment period	Time	Dichotomous Dummy	• 0 if in 6 month pre-treatment period • 1 if in 6 month post-treatment period
Study Group • Reference Group o XR-NTX • Comparison Groups o oral NTX o acamprosate o disulfiram o psychosocial therapy only	Treatment Type	Four Dichotomous Dummies	• Reference Group: XR-NTX • Dummy #1 o 1 if oral NTX, 0 else • Dummy #2 o 1 if acamprosate, 0 else • Dummy #3 o 1 if disulfiram, 0 else • Dummy #4 o 1 if psychosocial therapy, 0 else

Covariates. This analysis included covariates representing age, gender, beneficiary status, plan type, region, pre-treatment period mental health and substance abuse diagnoses, and pre-treatment period physical health diagnoses. The general risk adjustment strategy for this study followed Ettner et al,[42] which used demographics, mental health and substance abuse indicators, and either Adjusted Diagnostic Groups (ADGs) or Hierarchical Condition Categories (HCCs) to predict mental health and substance abuse spending among Michigan Medicaid enrollees. They found that mental health and substance abuse indicators were better predictors of mental health and substance abuse spending than physical health diagnoses. This risk adjustment strategy was selected since mental health and substance abuse diagnoses were expected to have high prevalence and strongly predict utilization and spending among the population of Aetna members with AUDs.

Demographics included in the model were age, gender, beneficiary status, plan type, and region. Age was categorized into a four-level categorical variable (younger than 35, 35 – 44, 45 – 54, 55 or older). Gender (M vs. F), beneficiary status (subscriber vs. dependent), and plan type (PPO vs. HMO) were dichotomous variables recorded in the claims data. Region of residence was a six-level categorical variable (West, Southwest, North Central, Southeast, Mid Atlantic, and Northeast) obtained from claims data.

Comorbidities were defined as physical health, mental health, or substance use disorders with which patients were diagnosed during the 6 month pre-treatment period. Diagnoses were grouped into mental health and substance abuse, or physical health categories by ICD-9 code. Following Ettner et al,[42] the mental health and substance abuse diagnoses were assigned to groups as defined by Dr. Michael First for use in the National Ambulatory Medical Care Survey.[43] The groups represented schizophrenia or other nonmood psychosis, bipolar disorder, major depression, anxiety disorder, and substance disorders. The substance abuse

indicator represented pre-treatment drug use disorder diagnoses. The groups were defined as follows:

Pre-Treatment Period Mental Health and Substance Abuse Indicators	
Categories	**ICD-9 Codes**
Schizophrenia or other non-mood	295, 297, 298
Bipolar disorder	296.0–296.1, 296.4–296.81, 296.89, 301.13
Major Depression	296.2–296.3
Anxiety disorders	300.0–300.09, 300.2–300.3, 308, 309.81, 309.89
Drug use disorders	292, 304, 305.2–305.7

The Charlson Comorbidity Index (CCI) was used to represent physical health comorbidities. Following D'Hoore et al,[44] physical health diagnoses made in the 6 month pre-treatment period were grouped by ICD-9 code into the 19 categories used to define the CCI. Each CCI category received a specified weight, and the weights were summed to create an overall CCI score for each patient. Due to low prevalence of physical health comorbidities in the study sample, the CCI score was collapsed into a three-level categorical variable (zero, 1-2, >2). The CCI groups are listed in the Appendix. Physical health, mental health, and substance abuse comorbidity variables are summarized below:

Pre-Treatment Comorbidity Indicator		**Categorical Levels**
Mental Health Indicators	Schizophrenia and other non-mood psychoses	0 No 1 Yes
	Bipolar Disorder	0 No 1 Yes
	Major Depression	0 No 1 Yes
	Anxiety Disorder	0 No 1 Yes
Substance Abuse Indicators	Drug Use Disorder	0 No 1 Yes
Physical Health Comorbidity Indicator	Charlson Comorbidity Index	0 Zero 1 1-2 2 >2

The broader categories of physical and mental health comorbidities were also used in the analysis. The dichotomous variable representing physical health comorbidities took the

value 1 if the Charlson score was greater than zero, and 0 if the Charlson score was zero. The dichotomous variable representing mental health comorbidities was 1 if the patient had a pre-treatment diagnosis of schizophrenia, bipolar disorder, major depression, or anxiety, and 0 otherwise.

STATISTICAL ANALYSIS

Specific Aim #1: Test the hypothesis that there is a difference in persistence between Aetna beneficiaries receiving XR-NTX vs. oral medications for alcohol use disorders (oral NTX, acamprosate, disulfiram).

Survival analysis compared persistence with XR-NTX vs. oral pharmacotherapies. The persistence outcome was treated as a continuous variable. It measured the number of consecutive days a patient was in possession of alcohol pharmacotherapy, beginning with the index date. Patients were considered to be in possession of medication for the duration of each successive prescription they filled, and were allowed ten days after each prescription expired to obtain a refill before being considered non-persistent. Non-persistence was the "failure event," and it was defined as allowing 10 days to elapse after a prescription had expired without refill. Persistence was defined as the number of days until the first episode of non-persistence. Any prescriptions filled after a patient first became non-persistent were not included in the analysis. No patients were censored prior to the end of the 180 day follow-up period, since follow-up was complete for six months after the index date. The primary predictor of interest was a treatment type categorical variable that was assigned the value 1 for those taking XR-NTX, 2 for those taking oral NTX, 3 for those taking acamprosate, and 4 for those taking disulfiram. Covariates included demographics (age, gender, region, plan type, beneficiary status), pre-treatment physical health comorbidities (Charlson score), and pre-treatment mental health and substance abuse indicators (schizophrenia, bipolar disorder, major depression, anxiety disorder, drug use

disorder). Kaplan-Meier survival curves plotted persistence over the 180 day follow-up period. The Cox proportional hazards model was used to compare the risk of discontinuation for (1) XR-NTX vs. oral pharmacotherapies, and (2) oral NTX vs. acamprosate and disulfiram.

Cost and Utilization Analysis: General Strategy

The exact model used to estimate cost and utilization depended on the nature of the dependent variables. An important econometric issue that arises when analyzing health care utilization and spending is that many people do not utilize or spend any money on health care in any given year. One well-validated approach used to assess health care utilization and spending is the two-part model.[45] In the first part of the two-part model, logistic regression is used to estimate the probability of any utilization or spending. In the second part, patients with nonzero costs/utilization of health care services are analyzed to estimate average costs/utilization conditional on use. Together, parts 1 and 2 provide an estimate of the average costs or utilization among all patients. This study employed the two-part model for all spending and utilization outcome variables.

The first part of the two-part model used logistic regression to estimate the effect of the predictor variables (four study group dummies, pre-treatment vs. post-treatment) on the probability that patients utilized health care services. The unit of observation was the half person-year. Multivariate regression controlled for covariate effects. Due to the nonlinearity of the logistic model, the effect of XR-NTX vs. comparison interventions could not be estimated directly from the interaction term coefficient.[46] Instead, simulation methods based on the estimated regression model calculated the average effect of the predictor variables on probability of utilization. Bootstrapping generated 95% confidence intervals.

The second part of the two-part model was restricted to those with nonzero health care utilization. This part of the analysis used regression techniques to model the outcome variables:

health care spending and utilization. The particular regression model depended on the nature of the outcome variable. Utilization outcomes that were measured by count variables (days in inpatient treatment, number of admissions, visits, and claims) required a negative binomial model. Spending outcomes were measured by continuous variables (costs) and required linear regression models. The independent variables included in the model were the same as in the first part of the two-part model.

However, there are important econometric issues that arise when considering health care spending. Even after excluding those who do not utilize any health care, the distribution of health care spending tends to be positively skewed. That is, a disproportionate few have high levels of spending. Traditionally, log transformation was used to address this concern. However, the back-transformation process is cumbersome. An alternative to the log transformation is the use of generalized linear models. This analysis used generalized linear models to address deviations from normality in the distribution of spending data. The generalized linear model approached used a logarithmic linking function, and the Park Test[45] was employed to determine the mean-variance relationship.

<u>Specific Aim #2:</u> Test the hypothesis that there is a difference in health care costs and utilization between Aetna beneficiaries receiving XR-NTX vs. comparison therapies.

The difference-in-differences method estimated the impact of XR-NTX vs. (1) oral NTX, (2) acamprosate, (3) disulfiram, and (4) psychosocial therapy only on health care costs and utilization. This technique compared the XR-NTX and comparison groups on the basis of the difference in health care costs and utilization that each group experienced in the six month period before vs. after treatment initiation. The primary predictors were (1) a time dummy variable that had the value 1 in the six month post-treatment period, and 0 in the six month pre-treatment period, and (2) four study group dummy variables. The interactions between the

time and study group dummy variables were also included, and they represented the difference-in-differences. Therefore, the four interaction terms were the primary estimands of interest, and they measured the difference (between XR-NTX and comparison groups) in the differences (between pre- and post-treatment). In all cases, the joint significance of the four study group dummy variables was calculated to assess the overall effect of treatment type on spending and utilization prior to conducting pairwise comparisons between XR-NTX and other study groups. Although not reported in the results, the four study group dummy variables were jointly significant in all models that were constructed. Covariates included in the model represented demographics (age, gender, region, plan type, beneficiary status).

Covariates representing pre-treatment physical health, mental health, and drug abuse diagnoses were found to interact strongly with the time dummy variable. Including comorbidities variables in the model without accounting for these interactions carried the implicit assumption that pre-treatment diagnoses predicted costs and utilization in the pre-treatment and post-treatment periods equally. This assumption was fallacious because pre-treatment diagnoses predicted costs and utilization in the pre-treatment period more strongly than the post-treatment period. Attempting to control for pre-treatment comorbidities without including interactions with the time dummy variable biased the estimated pre- vs. post-treatment difference in costs and utilization. Therefore, pre-treatment physical health, mental health, and drug abuse covariates were not included in the initial model. Stratified analyses were subsequently performed to assess interactions between comorbidities variables and the time dummy variable.

The two part model was used to estimate the difference-in-differences for (1) the probability of any utilization/spending, and (2) the average utilization/spending. The strength of this approach is that it accounts for time invariant differences between XR-NTX and comparison

groups. Its principal weaknesses are that it assumes (1) random allocation of treatment and (2) similar secular trends in all study groups.[47,48] In this observational study there was not random allocation of XR-NTX vs. comparison treatments. Comparability of the groups was addressed by controlling for demographics. In the next section, comparability is further addressed by performing stratified analyses over physical and mental health comorbidities variables.

Specific Aim #3: Test the hypothesis that pre-treatment physical and mental health comorbidities interact with time and treatment variables to predict health care costs and utilization.

Difference-in-difference-in-differences (DDD) analysis stratified the difference-in-differences estimates by the presence of (1) physical health comorbidities, and (2) mental health comorbidities. Thus, the change in costs and utilization between the pre- and post-treatment periods was estimated for those with pre-treatment comorbidities, and compared between the XR-NTX and comparison groups. The primary predictors were (1) a time dummy variable that had the value 1 in the six month post-treatment period, and 0 in the six month pre-treatment period, (2) four study group dummy variables, and (3) a dummy variable representing the presence of comorbidities. The comorbidities dummy variable took the value 1 for those with pre-treatment physical or mental health diagnoses, and 0 for those without pre-treatment diagnoses. Interactions between each of the treatment, time and comorbidities dummy variables were also included, as well as the triple interaction between all three. The triple interaction represented the DDD estimate, and it measured the difference (between those with vs. without pre-treatment comorbidities) in the difference (between XR-NTX and comparison groups) in the differences (between pre- and post-treatment). Again, the four study group dummy variables were jointly significant in all models. The two part model was used to estimate average utilization/spending per patient among the subsets with physical and mental health comorbidities.

III. RESULTS

DESCRIPTIVE STATISTICS

Aetna Behavioral Health extracted physical and behavioral health claims records from 5,141 patients diagnosed with alcohol use disorders who initiated medication-assisted treatment for alcohol dependence in 2007 – 2008: extended-release naltrexone (*n = 211*), oral naltrexone (*n = 1,408*), acamprosate (*n = 2,479*), and disulfiram (*n = 1,043*). The data set included a random sample of 6,374 control patients who initiated psychosocial therapy without medication assistance for alcohol use disorders during the same time period. The analysis describes differences between the study groups and compares months of continuous use of medication (persistence). Additional analyses assess the effect of treatment type on cost and utilization of physical and behavioral health services and the influence of physical and behavioral health comorbidities on cost and utilization.

Table 1 summarizes the characteristics of the five study groups. Overall, the sample included 62% men with a mean age of 41 years. Most had a PPO health plan (72%) and no physical health comorbitities (85%) or mental health comorbidities (79%). Four classes of mental health diagnoses were considered: schizophrenia; bipolar disorders; major depression; and anxiety disorders. Major depression (12%) was the most prevalent mental health diagnosis, followed by anxiety disorders (6%), bipolar disorder (5%), and schizophrenia (1%). Multiple mental health comorbidities were diagnosed in 4% of the study sample. Comorbid drug use disorders were diagnosed in 6% of patients.

Table 1. Descriptive Statistics

Variable		Study Group: XR-NTX *N* = 211	Oral NTX *N* = 1408	Acamprosate *N* = 2479	Disulfiram *N* = 1043	Psychosocial Therapy *N* = 6374	Chi-Squared	p-value
Gender (%)	Male	65.4	53.3	57.5	59.8	65.5	$\chi^2_{(4)} = 209$	< 0.001
Region (%)	West	11.4	13.7	15.2	21.3	8.3	$\chi^2_{(24)} = 2{,}100$	< 0.001
	Southwest	22.3	12.9	14.6	10.4	5.4		
	North Central	21.8	12.4	18.4	21.3	25.7		
	Southeast	13.3	15.3	21.2	15.6	8.7		
	Mid Atlantic	12.3	14.8	9.5	15.8	19.0		
	Northeast	18.9	30.8	21.0	15.6	32.9		
	Unknown	0.0	0.1	0.1	0.0	0.0		
Beneficiary Status (%)	Subscriber	63.0	58.2	64.6	65.3	58.9	$\chi^2_{(4)} = 76$	< 0.001
Plan Type (%)	PPO	100.0	66.1	65.0	68.0	76.2	$\chi^2_{(4)} = 468$	< 0.001
Age Groups (%)	< 35	23.2	30.3	17.1	21.6	37.0	$\chi^2_{(12)} = 836$	< 0.001
	35 – 44	35.1	27.3	27.2	29.9	24.0		
	45 – 54	30.8	27.8	37.2	34.1	25.7		
	55 or older	10.9	14.5	18.5	14.4	13.3		
Age ($M \pm sd$)		42.0 ± 11.2	40.5 ± 13.3	45.1 ± 10.9	43.4 ± 11.1	39.1 ± 14.4		
Charlson Comorbidity Index (CCI) Score Groups (%)	0	73.5	81.6	74.6	80.4	90.2	$\chi^2_{(8)} = 862$	< 0.001
	1 – 2	20.8	13.8	20.0	16.1	8.9		
	> 2	5.7	4.6	5.4	3.5	0.9		
Pre-Treatment Drug Abuse Diagnoses (%)	Drug Use Disorder	14.2	13.0	6.8	5.9	3.8	$\chi^2_{(4)} = 413$	< 0.001
Pre-Treatment Mental Health Diagnoses (%)	Schizophrenia	3.8	2.1	2.3	1.3	0.4	$\chi^2_{(4)} = 160$	< 0.001
	Bipolar Disorder	11.4	11.4	8.2	6.9	1.9	$\chi^2_{(4)} = 654$	< 0.001
	Major Depression	24.2	23.8	23.3	17.4	4.3	$\chi^2_{(4)} = 1{,}800$	< 0.001
	Anxiety Disorder	10.0	14.1	12.9	11.8	1.1	$\chi^2_{(4)} = 1{,}300$	< 0.001
	At least one	40.8	40.8	37.9	30.8	7.2	$\chi^2_{(4)} = 1{,}600$	< 0.001
	More than one	8.1	9.4	7.5	5.9	0.5	$\chi^2_{(4)} = 431$	< 0.001

Study groups significantly differed ($p < 0.001$) with respect to gender, age, geographic region of residence, plan type (HMO vs. PPO), beneficiary status (subscriber vs. dependent), and pre-treatment physical health, mental health, and substance abuse diagnoses.

Patients receiving psychosocial therapy only differed significantly from patients receiving medication-assisted treatment. Patients taking medications for alcohol use disorders were 57% male with an average age of 43 years. Two-thirds (67%) had PPO health plans, while 78% had no physical health comorbidities and 63% had no mental health comorbidities. Comorbid drug use disorders were diagnosed in 9% of patients receiving medication-assisted treatment. Each of these characteristics differed significantly ($p < 0.001$) from those listed in Table 1 for the psychosocial therapy only group. Patients receiving psychosocial therapy only were younger, more likely to be male, and less likely to have physical health, mental health, or

drug use disorder comorbidities. Among patients with physical or mental health comorbidities, those in the psychosocial therapy only group were less likely to have multiple diagnoses.

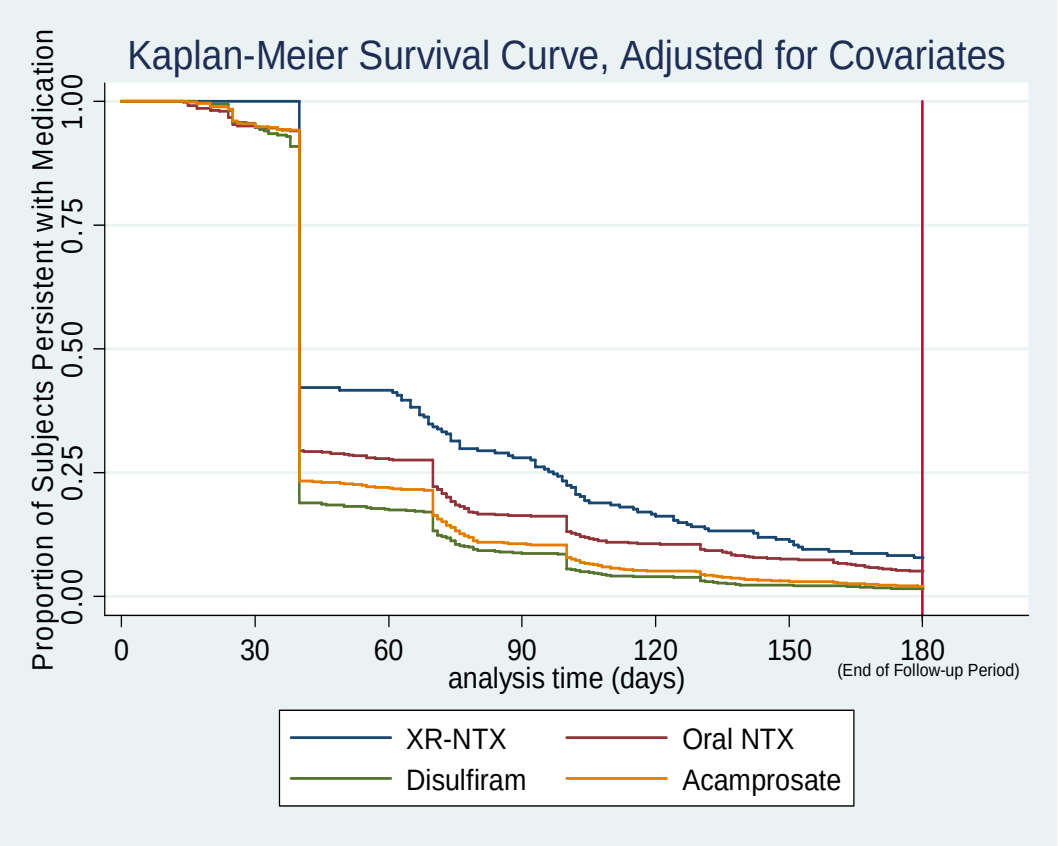
Among patients receiving medication-assisted treatment, those in the XR-NTX group were most likely to be male (65%) and have a PPO health plan (100%). Patients receiving acamprosate were the oldest (*M = 45 years*) and patients taking oral NTX were the youngest (*M = 40.5 years*). The XR-NTX and acamprosate groups had the highest prevalence of pre-treatment physical health comorbidities (25%), while the XR-NTX and oral NTX groups had the highest prevalence of mental health (41%) and drug abuse (14%) comorbidities.

PERSISTENCE RESULTS

Survival analysis assessed the duration of alcohol pharmacotherapy. Patients were considered to be non-persistent the first time they allowed ten days to elapse after a prescription had expired without obtaining a refill. The ten day "grace period" was introduced because prescriptions were not always refilled immediately. Figure 1 displays a Kaplan-Meier curve plotting the proportion of patients who filled prescriptions over time. Most (89%) patients began their treatment with 30-day prescriptions. Smaller proportions of patients began treatment with shorter (8%) or longer (3%) prescriptions. Each study group had a steep drop in persistence at 40 days (the first time patients with 30-day prescriptions could "fail" to refill). Approximately 40% of XR-NTX patients filled a second prescription, as opposed to 30% of oral NTX patients, 25% of acamprosate patients, and 20% of disulfiram patients. Nearly 30% of all XR-NTX patients filled a third prescription, compared to 20% of oral NTX patients and 10 – 15% of acamprosate and disulfiram patients. The survival curves leveled out around 90 – 120 days (three to four prescriptions for most patients), suggesting that patients who filled prescriptions

regularly for three to four months continued to fill prescriptions beyond that time. The XR-NTX group had the highest level of persistence (15%) at the end of the six-month follow-up period.

Figure 1. Persistence with Medication over Time[a]



[a] Survival curves are adjusted for demographics (gender, age, region, beneficiary status, plan type), pre-treatment physical health comorbidities (Charlson score), pre-treatment drug abuse comorbidities, and pre-treatment mental health comorbidities (schizophrenia, bipolar, major depression, anxiety).

Cox proportional hazards regression compared the risk of non-persistence for (1) XR-NTX vs. oral pharmacotherapies, and (2) oral NTX vs. acamprosate and disulfiram. The results are summarized in Table 2. The analysis controlled for demographics, physical health comorbidities, mental health comorbidities, and drug abuse comorbidities. Patients taking XR-NTX were more likely to persist with treatment than patients taking oral medications. Throughout the six-month follow-up period, patients taking oral NTX, disulfiram, and

acamprosate were 27%, 47%, and 49% more likely to discontinue treatment (fail to refill a prescription) than XR-NTX patients, respectively.

Table 2. Persistence Survival Analysis to compare the risk of failing to refill prescriptions among medication groups over the six-month follow-up period[a]

Treatment Group	Comparison to XR-NTX Hazard Ratio (95% CI)	Comparison to Oral NTX Hazard Ratio (95% CI)
XR-NTX	Ref.	0.79 (0.70 to 0.89)
Oral NTX	1.27 (1.12 to 1.43)	Ref.
Disulfiram	1.47 (1.30 to 1.66)	1.16 (1.09 to 1.23)
Acamprosate	1.49 (1.32 to 1.67)	1.17 (1.11 to 1.23)

[a] Cox proportional hazards model includes covariates representing demographics (gender, age, region, plan type, beneficiary status), pre-treatment medical comorbidities (Charlson score), pre-treatment mental health comorbidities (schizophrenia, bipolar, major depression, anxiety), and pre-treatment substance abuse comorbidities (alcohol and drug use disorders).

** Indicates $p < 0.05$

Moreover, patients taking oral NTX were more likely to persist with treatment than patients taking acamprosate or disulfiram. Those taking disulfiram and acamprosate were 16% and 17% more likely to discontinue treatment than those taking oral NTX, respectively. This suggests a drug effect (those taking oral or extended-release naltrexone persisted with treatment longer than those taking acamprosate or disulfiram) as well as a naltrexone delivery effect (those receiving XR-NTX persisted longer than those taking oral NTX).

COST AND UTILIZATION RESULTS

Spending and Utilization Outcomes in the Full Study Sample

Difference-in-differences analysis evaluated changes in non-pharmacy health care spending and utilization between the pre- and post-treatment periods, and compared them between study groups. XR-NTX was the focus of the study, so comparisons were limited to XR-NTX vs. comparison groups. Table 4 reports mean spending and utilization per patient in the pre- and post-treatment periods, post- vs. pre-treatment differences, and comparisons of the pre/post differences between the XR-NTX and comparison groups. All analyses controlled for demographics. Total non-pharmacy spending, inpatient admissions, and inpatient days include both physical and behavioral health components.

Table 4. Average Spending and Utilization per Patient in the Full Study Sample, Aggregated Over Six Months[a]

Time Period	Study Group	N	Outpatient Psychosocial Therapy Visits	Outpatient Behavioral Health Hospital Visits	Inpatient Admissions	Inpatient Days	ER Visits	Non-Pharmacy Spending ($)
Pre-Treatment Period	XR-NTX	211	2.85	2.89	1.06	4.66	0.75	7,882
	Oral NTX	1,408	2.74	2.14	0.63	3.17	0.62	7,131
	Acamprosate	2,479	1.77	1.48	0.74	3.28	0.63	6,371
	Disulfiram	1,043	2.01	1.64	0.43	1.74	0.49	5,208
	Psychosocial Therapy Only	6,374	0.01	1.41	0.56	2.37	0.49	3,807
Post-Treatment Period	XR-NTX	211	3.74	4.05	0.54	1.91	0.51	5,730
	Oral NTX	1,408	3.52	3.77	0.41	1.84	0.44	6,326
	Acamprosate	2,479	2.72	3.89	0.50	1.89	0.46	6,022
	Disulfiram	1,043	2.64	3.32	0.29	0.99	0.38	4,587
	Psychosocial Therapy Only	6,374	0.04	6.28	0.49	1.94	0.32	4,333
Post- vs. Pre-Treatment Difference (95% CI)	XR-NTX	211	0.89** (0.23 to 1.61)	1.16 (−0.45 to 2.41)	−0.52 (−0.89 to 0.03)	−2.75** (−4.84 to −1.42)	−0.24 (−0.43 to 0.02)	−2,152** (−3,957 to −466)
	Oral NTX	1,408	0.78** (0.48 to 1.08)	1.63** (1.12 to 2.18)	−0.22** (−0.32 to −0.09)	−1.33** (−1.76 to −0.90)	−0.18** (−0.24 to −0.11)	−805 (−1,530 to 6)
	Acamprosate	2,479	0.95** (0.78 to 1.13)	2.41** (2.04 to 2.76)	−0.24** (−0.35 to −0.16)	−1.38** (−1.67 to −1.02)	−0.17** (−0.22 to −0.12)	−349 (−926 to 108)
	Disulfiram	1,043	0.63** (0.26 to 0.92)	1.68** (1.18 to 2.33)	−0.14* (−0.26 to −0.01)	−0.75** (−1.25 to −0.37)	−0.11** (−0.19 to −0.06)	−621 (−1,422 to 41)
	Psychosocial Therapy Only	6,374	0.03** (0.01 to 0.06)	4.87** (4.57 to 5.17)	−0.07* (−0.13 to −0.00)	−0.42** (−0.71 to −0.16)	−0.17** (−0.20 to −0.15)	526** (195 to 733)
Change in XR-NTX Relative to Change in Comparison Group (95% CI)	Oral NTX		0.11 (−0.67 to 0.88)	−0.47 (−1.96 to 0.91)	−0.30 (−0.70 to 0.21)	−1.42* (−3.39 to −0.02)	−0.06 (−0.25 to 0.20)	−1,347 (−3,487 to 546)
	Acamprosate		−0.06 (−0.80 to 0.56)	−1.25* (−3.05 to −0.08)	−0.28 (−0.65 to 0.32)	−1.37 (−3.41 to 0.01)	−0.07 (−0.26 to 0.18)	−1,803 (−3,541 to 71)
	Disulfiram		0.26 (−0.57 to 0.95)	−0.52 (−1.92 to 0.72)	−0.38 (−0.81 to 0.14)	−2.00** (−4.11 to −0.62)	−0.13 (−0.32 to 0.13)	−1,531 (−3,337 to 546)
	Psychosocial Therapy Only		0.86** (0.19 to 1.57)	−3.71** (−5.30 to −2.65)	−0.45 (−0.83 to 0.08)	−2.33** (−4.21 to −0.94)	−0.07 (−0.25 to 0.17)	−2,678** (−4,430 to −960)

[a] Model contains all demographics (gender, age, region, beneficiary status, plan type), treatment group, time relative to index date, and the treatment*time interaction.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Average pre-treatment spending and utilization of outpatient psychosocial therapy (psychiatrist and therapist visits), outpatient behavioral health hospital/inpatient facility services, inpatient services, and emergency services were higher in the XR-NTX group than all comparison groups. Psychosocial therapy only patients had very low utilization of outpatient behavioral health services in the pre- and post-treatment periods, but their utilization of hospital services (inpatient and outpatient) was higher than any other study group in the post-treatment period. In the post-treatment period, utilization of health care services remained

higher in the XR-NTX group than oral pharmacotherapy groups, but average spending among XR-NTX patients was lower than acamprosate or oral NTX.

All study groups experienced significant ($p < 0.01$) increases in the average number of outpatient psychosocial therapy visits following treatment initiation. Increases were on the order of one additional therapist or psychiatrist visit over six months for every 1 to 2 patients in the medication-assisted groups, and one additional visit for every 25 patients in the psychosocial therapy only group. The increases in utilization of outpatient psychosocial therapy did not significantly differ between the XR-NTX and oral pharmacotherapy groups, but the increase in the XR-NTX group was significantly greater ($p < 0.01$) than the psychosocial therapy only group.

Behavioral health outpatient utilization of hospital/inpatient facility services (intensive outpatient treatment, partial hospitalization) increased in the post-treatment period for all study groups. Increases were on the order of one additional visit over six months per XR-NTX patient, 1.5 to 2 additional visits per oral pharmacotherapy patient ($p < 0.01$), and nearly 5 additional visits per psychosocial therapy only patient ($p < 0.01$). XR-NTX patients decreased utilization of behavioral health outpatient hospital services relative to all comparison groups, and the relative decreases were significant compared to acamprosate ($p < 0.05$) and psychosocial therapy only ($p < 0.01$).

Utilization of inpatient hospital and emergency room (ER) services decreased following treatment initiation in all study groups, more so for XR-NTX patients than comparison patients. All decreases were significant except for inpatient admissions and ER visits among XR-NTX patients, despite larger decreases in the XR-NTX group than the comparison groups. Decreases in inpatient utilization were on the order of one admission (average length of stay: 5 to 6 days) over six months for every two XR-NTX patients, four oral NTX and acamprosate patients, seven disulfiram patients, and 14 psychosocial therapy only patients. Decreases in ER utilization were

on the order of one visit over six months for every four XR-NTX patients, six oral NTX, acamprosate, or psychosocial therapy only patients, and nine disulfiram patients. Relative decreases in the XR-NTX vs. comparison groups were nonsignificant with respect to inpatient admissions and ER visits. The XR-NTX relative decrease in inpatient days was significant compared to oral NTX ($p < 0.05$), disulfiram ($p < 0.01$), and psychosocial therapy only ($p < 0.01$).

Non-pharmacy health care spending decreased significantly in the post-treatment period for the XR-NTX group ($p < 0.01$) and nonsignificantly for the oral medication groups, but increased significantly for the psychosocial therapy only group ($p < 0.01$). Average health care spending per patient decreased to a greater extent in the XR-NTX group than any comparison group. Over six months, the XR-NTX group decreased average spending by $1,300 to $1,800 per patient more than oral medication groups ($p > 0.05$), and nearly $2,700 per patient more than the psychosocial therapy only group ($p < 0.01$).

Total non-pharmacy spending and inpatient utilization outcomes combined physical and behavioral health claims. In general, changes in physical and behavioral health spending and inpatient utilization were complementary (See Appendix). Physical and behavioral health inpatient utilization decreased in each study group. All medication-assisted study groups experienced concomitant decreases in physical and behavioral health spending. Psychosocial therapy only patients decreased mean physical health spending by $480 per patient ($p < 0.01$) and increased mean behavioral health spending by $970 per patient ($p < 0.01$) over six months.

Subset Analyses: Patients with Comorbidities. Difference-in-difference-in-differences analyses assessed the impact of pre-treatment physical and mental health comorbidities on health care spending and utilization. The difference-in-differences analysis of the full study sample was stratified by the presence of physical and mental health comorbidities. Stratum-specific

estimates of the post- vs. pre-treatment differences in average utilization and spending were calculated and compared between the XR-NTX and comparison groups. Comparisons of the pre/post differences between the XR-NTX and comparison comorbidities subsets are presented in Table 5. There were too few psychosocial therapy only patients with any psychosocial therapy visits in the subsets with physical (*n = 0*) and mental health (*n = 7*) comorbidities to include them in the model.

Table 5. Comorbidities Subset Analyses: Change in Average Six-Month Utilization and Spending in XR-NTX Group Relative to Comparison Groups (95% CI)

Comorbidities Subset	Comparison Group	N	Outpatient Psychosocial Therapy Visits	Outpatient Behavioral Health Hospital Visits	Inpatient Admissions	Inpatient Days	ER Visits	Non-Pharmacy Spending ($)
Patients with Pre-Treatment Physical Health Comorbidities[a] (XR-NTX: N = 56)	Oral NTX	259	−0.53 (−1.83 to 1.45)	−0.90 (−4.94 to 3.12)	−0.90** (−1.51 to −0.37)	−4.03** (−6.64 to −2.00)	−0.70** (−1.36 to −0.15)	−5,820** (−10,180 to −1,733)
	Acamprosate	629	−0.33 (−1.57 to 1.51)	−1.08 (−5.48 to 3.46)	−0.55 (−1.07 to 0.03)	−2.91* (−5.31 to −0.84)	−0.58* (−1.22 to −0.02)	−4,598** (−7,909 to −1,327)
	Disulfiram	205	−0.10 (−1.31 to 2.35)	−0.11 (−3.98 to 4.48)	−0.75* (−1.27 to −0.09)	−2.40* (−5.09 to −0.08)	−0.53 (−1.18 to 0.16)	−3,454 (−7,529 to 62)
	Psychosocial Therapy Only	626	----	−2.31 (−5.78 to 1.98)	−0.49 (−0.97 to 0.05)	−2.72* (−5.21 to −0.50)	−0.56* (−1.21 to −0.02)	−3,463* (−6,852 to −254)
Patients with Pre-Treatment Mental Health Comorbidities[a] (XR-NTX: N = 86)	Oral NTX	574	0.00 (−1.43 to 1.72)	−0.38 (−3.08 to 2.73)	−0.34 (−0.92 to 0.77)	−3.38** (−6.89 to −0.84)	−0.20 (−0.65 to 0.30)	−4,214** (−7,543 to −923)
	Acamprosate	939	−0.31 (−1.80 to 1.32)	−0.88 (−3.80 to 2.11)	−0.10 (−0.70 to 0.99)	−2.93* (−6.68 to −0.66)	−0.16 (−0.64 to 0.35)	−4,029** (−7,186 to −1,020)
	Disulfiram	321	0.05 (−1.57 to 2.04)	0.28 (−2.42 to 3.34)	−0.27 (−0.92 to 0.68)	−3.73** (−7.25 to −0.91)	−0.28 (−0.75 to 0.29)	−2,671 (−5,838 to 428)
	Psychosocial Therapy Only	457	----	−1.38 (−4.49 to 1.30)	−0.22 (−0.42 to 1.47)	−1.04 (−4.91 to 1.09)	0.19 (−0.31 to 0.72)	−1,115 (−4,688 to 1,775)

[a] Models contain all demographics, treatment group, time relative to index date, comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities. Physical health comorbidities are present if Charlson score > 0. Mental health comorbidities include schizophrenia, bipolar disorder, major depression, and anxiety disorders.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Average pre-treatment health care utilization and spending were greater in the physical and mental health comorbidities subsets than the full study sample (See Appendix). Within the comorbidities subsets, patients receiving XR-NTX decreased non-pharmacy health care spending relative to comparison groups to a greater extent than in the full sample. XR-NTX patients with physical health comorbidities (Charlson Comorbidity Index > 0) decreased health care expenses by approximately $5,800 and $4,600 per patient ($p < 0.01$) over six months compared to similar oral NTX and acamprosate patients, respectively. They also decreased health care spending by

$3,500 per patient over six months compared to psychosocial therapy only ($p < 0.05$) and disulfiram (nonsignificant). Spending decreases in the XR-NTX physical health comorbidities subset relative to comparison groups were accompanied by significant relative decreases in utilization of inpatient and emergency services, and nonsignificant relative decreases in utilization of outpatient psychosocial therapy as well as utilization of outpatient behavioral health hospital/facility services.

XR-NTX patients with mental health comorbidities (diagnoses of schizophrenia, bipolar disorder, major depression, or anxiety disorders) decreased non-pharmacy health care spending by approximately $4,000 per patient ($p < 0.01$) over six months compared to similar oral NTX and acamprosate patients, $2,700 per patient compared to disulfiram patients (nonsignificant), and $1,100 per patient compared to psychosocial therapy only patients (nonsignificant). Spending decreases in the XR-NTX mental health comorbidities subset relative to comparison groups were accompanied by significant relative decreases in inpatient days, and nonsignificant relative decreases in inpatient admissions, ER visits, behavioral health outpatient hospital visits, and outpatient psychosocial therapy visits.

IV. DISCUSSION

DESCRIPTIVE STATISTICS

Aetna Behavioral Health provided claims data from their nationwide database to examine persistence with medication for alcohol use disorders as well as health care costs incurred among patients receiving different treatments for alcohol addiction. Study patients were drawn from a "real world" population, meaning that patients received alcohol pharmacotherapy based on the clinical judgment of their regular providers. Descriptive findings suggest that alcohol pharmacotherapies were prescribed to older and sicker patients than patients receiving psychosocial therapy alone. Among patients who received alcohol pharmacotherapies, those prescribed XR-NTX were sicker, more likely to be male, and more likely to have PPO health plans than those prescribed oral medications. All patients who received XR-NTX were in PPO health plans, suggesting that the price of the drug (approximately $700 per month) has discouraged its use in capitated health plans.

Although direct measures of alcohol addiction severity were not available, components of the Charlson Comorbidity Index and descriptive cost and utilization data provided indirect evidence. Across study groups, the most prevalent physical health diagnoses that were captured in the Charlson score were alcohol withdrawals (7.3%) and liver disease (2.7%). XR-NTX patients had the highest prevalence of pre-treatment alcohol withdrawal (15.6%) and liver disease (5.7%) diagnoses, suggesting more severe alcohol addiction. Descriptive cost and utilization data also supports the idea that XR-NTX patients had more severe alcohol addiction than patients receiving oral pharmacotherapies or psychosocial therapy only. XR-NTX patients had higher pre-treatment utilization of inpatient and outpatient behavioral health services than any other group. Similar findings were observed for utilization of pre-treatment physical health

services, which suggests that XR-NTX patients were sicker than those receiving oral pharmacotherapy or psychosocial therapy only prior to treatment initiation.

PERSISTENCE

Patients taking XR-NTX persisted with treatment longer than patients receiving oral pharmacotherapies, controlling for demographics and pre-treatment physical health, mental health, and substance abuse comorbidities. This finding is remarkable, since XR-NTX patients had a high prevalence of pre-treatment comorbidities that were expected to make persistence more difficult. Both oral NTX and XR-NTX patients persisted with treatment significantly longer than acamprosate and disulfiram patients, suggesting a naltrexone drug effect. Furthermore, XR-NTX patients persisted with treatment significantly longer than oral NTX patients, suggesting a naltrexone delivery mode effect.

Over 50% of patients in all study groups filled only the index prescription that was required for inclusion in the study, and failed to fill a second prescription. In fact, only 40% of XR-NTX patients and approximately 25% of oral pharmacotherapy patients filled a second prescription. It appears that the benefit in persistence among XR-NTX patients compared to oral pharmacotherapy lies in the higher probability of filling a second prescription. After the second month, the difference in persistence between XR-NTX and oral pharmacotherapy patients diminished over the six-month follow-up period. However, the XR-NTX group maintained higher persistence than any other study group at the end of the six month study period. This pattern may suggest that less motivated patients or those with barriers to persistence who received oral pharmacotherapies stopped filling prescriptions almost immediately, whereas less motivated patients receiving XR-NTX took longer to drop out.

However, the persistence outcome needs to be interpreted carefully, since no direct information regarding health outcomes is available. Further research is needed to examine the impact of persistence on alcohol-related health outcomes such as heavy drinking and abstinence. Persistence with medication throughout the brief six-month follow-up period would be associated with improved drinking outcomes if (1) patients took the medications they purchased, and (2) the medications were efficacious. The efficacy of these medications has been established in the literature, but persistence does not guarantee that patients in the oral medication groups actually swallowed the pills they purchased. One nice property of XR-NTX in this regard is that it is generally administered in a doctor's office, such that persistence with XR-NTX means that the patients truly took the drug as prescribed. Therefore, persistence may overestimate adherence in the oral pharmacotherapy groups, but persistence should be equivalent to adherence in the XR-NTX group.

One further consideration is that nonpersistence may not always be associated with poor drinking outcomes. In particular, individuals who are doing well after one or two months of treatment may decide to discontinue their medication, feeling that they no longer need it. This effect could be particularly important in the XR-NTX group, since treatment is quite expensive (approximately $700 per month). Therefore, some proportion of XR-NTX patients who became nonpersistent are likely to be those who demonstrated the greatest clinical improvement in the shortest amount of time, such that continuing to pay for expensive treatment may not seem worth it.

COST AND UTILIZATION

Although direct health outcomes were not available in this study, cost and utilization outcomes were. Average non-pharmacy health care spending per individual was the primary outcome of

interest, supplemented by inpatient admissions and days, ER visits, and outpatient behavioral health psychosocial therapy and hospital visits. Table 6 summarizes the spending and utilization changes that occurred with XR-NTX treatment relative to other study groups.

Table 6. Summary of Cost and Utilization of Health Care Services in the XR-NTX Group Relative to Other Groups

Sample	Comparison Group	N	Change in XR-NTX Group Relative to Change in Comparison Groups: Outpatient Psychosocial Therapy Visits	Outpatient Behavioral Health Hospital Visits	Inpatient Admissions	Inpatient Days	ER Visits	Non-Pharmacy Health Care Spending
Full Study Sample (XR-NTX: N = 211)	Oral NTX	1,408	↑	↓	↓	↓	↓	↓
	Acamrosate	2,479	↓	↓	↓	↓	↓	↓
	Disulfiram	1,043	↑	↓	↓	↓↓	↓	↓
	Psychosocial Therapy Only	6,374	↑↑	↓↓	↓	↓↓	↓	↓↓
Physical Health Comorbidities Subset (XR-NTX: N = 56)	Oral NTX	259	↓	↓	↓↓	↓↓	↓↓	↓↓
	Acamrosate	629	↓	↓	↓	↓	↓	↓↓
	Disulfiram	205	↓	↓	↓	↓	↓	↓
	Psychosocial Therapy Only	626	----	↓	↓	↓	↓	↓
Mental Health Comorbidities Subset (XR-NTX: N = 86)	Oral NTX	574	↑	↓	↓	↓↓	↓	↓↓
	Acamrosate	939	↓	↓	↓	↓	↓	↓↓
	Disulfiram	321	↑	↑	↓	↓↓	↓	↓
	Psychosocial Therapy Only	457	----	↓	↓	↓	↑	↓

↓	Nonsignificant decrease in XR-NTX group relative to comparison group
↓	Significant ($p < 0.05$) decrease in XR-NTX group relative to comparison group
↓↓	Highly significant ($p < 0.01$) decrease in XR-NTX group relative to comparison group

In the full sample, patients in the XR-NTX group decreased their average non-pharmacy health care spending and utilization relative to oral pharmacotherapies and psychosocial therapy only. Restriction to patients with pre-treatment physical and mental health comorbidities yielded larger relative decreases in mean health care costs and utilization in the XR-NTX group compared to other study groups. The subset analyses were more significant than the full sample comparisons despite smaller sample sizes. These finding echo work done by Weisner and colleagues that demonstrated improvements in cost-effectiveness with integrated

primary care and substance abuse treatment, but only for individuals with substance abuse-related medical conditions.[40]

Non-pharmacy health care spending decreased in the post-treatment period for the majority of groups in the full sample and subset analyses. For all groups, spending decreases were driven by decreased average spending among those with nonzero expenses (part 2 of two-part model) more so than increases in the proportion of patients with zero spending (part 1 of two-part model), although both occurred (See Appendix). Spending decreases were attended by decreases in inpatient admissions, inpatient days, and ER visits. In all groups, the decreased utilization of inpatient and ER services was driven by decreases in the proportion of patients with any utilization more so than changes in average utilization conditional on use. Therefore, there was a net increase in the proportion of patients with zero utilization of inpatient and emergency services.

In spite of the spending decreases, utilization of outpatient behavioral health services increased in all groups, both in the full sample and the comorbidities subsets. The increased utilization of outpatient behavioral health services consisted of increases in psychosocial therapy (psychiatrist and therapist visits) and increases in behavioral health outpatient hospital/facility visits (intensive outpatient treatment, partial hospitalization). Increases in utilization of outpatient behavioral health services suggest that on average patients received more outpatient substance abuse treatment in the post-treatment period than the pre-treatment period. This indicates that the observed decreases in utilization of inpatient and emergency services do not mean that patients were being lost to the health care system, since they continued to show up for outpatient behavioral health treatment.

There is further evidence to suggest that the patients were not simply avoiding health care in the post-treatment period. In terms of non-pharmacy spending, 97% – 98% of each pharmacotherapy group had nonzero health care spending in the pre-treatment period, which decreased to 90% – 95% in the post-treatment period. Even in the post-treatment period, a strong majority of patients receiving pharmacotherapy utilized health care services. Combined with the finding that utilization of inpatient and emergency health care services decreased considerably in the post-treatment period, these results suggest that patients continued to utilize outpatient services while decreasing their inpatient and emergency utilization. The psychosocial therapy only group had lower proportions of patients with nonzero health care spending in the pre-treatment (87%) and post-treatment (74%) periods, which corresponds to the relative health of those patients.

COMPARISON WITH PREVIOUS STUDIES

This is the first study to date that has examined the influence of XR-NTX on persistence as well as health care spending and utilization outcomes. However, a handful of recent studies have examined persistence[18,37,38] and health care costs and utilization[39] among individuals receiving oral NTX. The current study demonstrated similar persistence, utilization, and spending patterns to previous findings, but found lower levels of persistence. Lower levels of persistence in the current study may be attributable to a more stringent definition of persistence. Furthermore, differences in persistence may reflect differences in the health of the populations or unique features of the Aetna Behavioral Health system. Spending outcomes differed from the Kranzler et al study[39] of oral NTX spending and utilization because this study did not include pharmacy costs in its analyses, but overall patterns were similar.

STRENGTHS AND LIMITATIONS

This study has several strengths in its design and analytic approach. The data comes from Aetna's nationwide claims and utilization database, which provides a geographically diverse sample of patients as well as accurate cost and utilization information. All patients included in the study are members of Aetna Behavioral Health. This ensures that each patient's health care is coordinated through a business with guiding principles, financial incentives, and organizational structure that are representative of private health insurance companies throughout the United States. All patients included in the study were enrolled with Aetna for at least six months before and after treatment initiation, which guarantees there are no censored observations and strengthens the internal validity of the analyses. The study sample was drawn from a "real world" population, meaning that descriptive demographic, cost, and utilization statistics are representative of the people who are receiving each alcohol pharmacotherapy in actual clinical practice. Survival analysis provided temporal data on persistence with medication throughout the six-month follow-up period. Finally, the difference-in-differences analytic approach minimizes the effects of unmeasured confounding factors. It controls for time-independent baseline differences in cost and utilization by taking the pre- vs. post-treatment differences for each comparison group. Potential confounders that prior studies have identified as particularly important to our research question are explicitly accounted for in the multivariate models.

In addition to its strengths, the study was subject to several limitations that must be acknowledged. First, treatment was not randomly allocated. Each patient received the form of treatment that his or her providers thought was most appropriate or would produce the most favorable clinical response. Based on the descriptive statistics, these decisions appear to have been influenced by demographic features, comorbid diagnoses, and the level of utilization of

pre-treatment health care services. The decisions were also most likely influenced by factors that were not recorded in the Aetna claims database, and therefore unavailable for this study. Available covariates were taken into account as potential confounders or effect modifiers, but it is difficult to disentangle the effects of the drugs from the effects of other factors that could have influenced treatment selection and outcomes.

Perhaps the most important variables that were not available were those representing alcohol use disorder severity and psychometrics such as motivation to change drinking behavior. There were indirect measures of severity such as pre-treatment alcohol withdrawals, liver disease, and utilization of behavioral health services. These indirect measures provide some information on severity of alcohol addiction, but their accuracy and precision are limited. Nonetheless, severity and motivation to quit are likely to be negative confounders of the persistence and cost/utilization results that compare XR-NTX to other study groups, thereby biasing the results towards the null. Severity of alcohol addiction and low motivation to quit are expected to be associated with XR-NTX treatment as well as poor persistence and poor response to treatment, leading to relatively high costs in the post-treatment period.

Another potentially important unmeasured confounder might be utilization of out-of-plan services such as community-based 12-step programs. Use of out-of-plan services in addition to pharmacotherapy may be a marker for increased addiction severity in this insured population, and would thus likely differentially affect those prescribed XR-NTX, potentially contributing to increased persistence and decreased costs in this group.

Complete pharmacy claims data were not available, which is a limitation because of the high price of XR-NTX relative to other alcohol medications. In the Aetna study sample, the average cost of 30-day prescriptions for XR-NTX, oral NTX, acamprosate, and disulfiram were $696, $76, $82, and $62, respectively. For each month of medication, XR-NTX patients spent

approximately $600 more than oral medication patients, and $700 more than psychosocial therapy only patients. Relative non-pharmacy cost decreases in the XR-NTX group versus comparison groups appear to be on the order of the excess cost of XR-NTX pharmacotherapy, particularly in the comorbidities subset. Further research is needed to address the effects of persistence and drug prices on health care spending and utilization.

This study is also limited by statistical concerns. First, multiple cost and utilization comparisons raises the possibility of type I error. Second, the small sample size of the XR-NTX group (*n = 211*) and the large variances in the spending outcomes limit the power of the study, raising the possibility of type II error. However, the consistency of the results across several outcomes increases confidence that the observed differences are real. For each group, decreases in spending are generally associated with coincident decreases in admissions, inpatient days, and ER visits. Difference-in-difference estimates comparing XR-NTX to other study groups were consistent across all spending and utilization outcomes. It is highly unlikely that such consistency would be observed if the results were attributable to chance.

The possibility of regression to the mean cannot be ruled out. The six-month pre- and post-treatment periods are fairly short, and may not accurately capture fluctuations in spending and utilization that occur over time. If treatment were preferentially initiated after particularly costly episodes of bad health or poorly controlled alcohol addiction, then the patients may naturally tend to stabilize following treatment and incur fewer costs. Regression to the mean is a possibility that cannot be ignored, but it is unlikely to account for the observed differences between XR-NTX and other groups. In fact, since XR-NTX treatment is most likely associated with relatively severe alcohol addiction, it is unlikely that XR-NTX patients would respond to a clinical crisis more quickly or to a greater extent than those with less severe alcoholism. In the

absence of medication, the XR-NTX patients would be expected to take longer to clinically stabilize following a crisis than patients from other groups.

Finally, secular trends may have affected the results of the study. The study period approximately corresponds to the time frame of the national economic recession, such that the entire study may be influenced by forces unique to that period of time in American history.

V. SUMMARY AND CONCLUSIONS

Patients with alcohol use disorders who were prescribed XR-NTX persisted with treatment longer and experienced decreases in non-pharmacy physical and behavioral health spending and utilization relative to those who receive oral pharmacotherapies or psychosocial therapy only. Patients with physical and mental health comorbidities appear to experience particularly large decreases in health care spending and utilization with XR-NTX. Despite its high price, this study provides evidence that XR-NTX is associated with considerable savings in physical as well as behavioral health care costs. Treatment with XR-NTX may be most appropriate in patients who have comorbid diagnoses or encounter difficulty adhering to treatment with oral medications. Future research on this topic is necessary to clarify the associations between persistence, health care spending & utilization, and health outcomes such as heavy drinking and abstinence. Cost-effectiveness analyses of XR-NTX and oral medications would provide critical information for practicing clinicians and insurance providers. Most importantly, future research should focus on developing strategies for reducing barriers to medication-assisted treatment for alcohol abuse.

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VII. APPENDIX

Table A1. Charlson Comorbidity Index Coding

Weights	Categories	ICD-9 Codes
1	Myocardial Infarction	410, 411
	Congestive Heart Failure	398, 402, 428
	Peripheral Vascular Disease	440 – 447
	Dementia	290, 291, 294
	Diabetes Mellitus	250 (excluding 250.4 – 250.6)
	Cerebrovascular Disease	430 – 433, 435
	Chronic Pulmonary Disease	491 – 493
	Connective Tissue Disease	710, 714, 725
	Ulcer Diagnosis	531 – 534
	Mild Liver Disease	571, 573
2	Hemiplegia	342, 434, 436, 437
	Diabetes with end organ disease	250.4 – 250.6
	Moderate or severe renal disease	403, 404, 580 – 586
	Any tumor	140 – 195
	Leukemia	204 – 208
	Lymphoma	200, 202, 203
3	Moderate or severe liver disease	070, 570, 572
6	AIDS	042 – 044
	Metastatic solid tumor	196 – 199

Table A2. Physical and Behavioral Health Non-Pharmacy Costs in the Full Sample[a]

Variables			Percentage of Patients with Any Spending (%)				Average Spending Per Patient Among Those with Nonzero Spending ($)			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Total Non-Pharmacy Costs	XR-NTX	211	96.7	95.3	−1.4 (−5.9 to 2.0)	----	8,147	6,009	−2,138* (−3,813 to −245)	----
	Oral NTX	1,408	97.4	93.1	−4.3** (−6.1 to −3.0)	2.9 (−1.1 to 6.7)	7,318	6,786	−532 (−1,302 to 357)	−1,606 (−3,652 to 361)
	Acamprosate	2,479	97.9	93.6	−4.3** (−5.4 to −3.0)	2.9 (−1.7 to 6.4)	6,504	6,421	−83 (−683 to 382)	−2,055* (−3,657 to −173)
	Disulfiram	1,043	97.1	90.5	−6.6** (−8.8 to −4.7)	5.2* (1.2 to 9.7)	5,359	5,057	−302 (−1,113 to 418)	−1,836 (−3,666 to 255)
	Psychosocial Therapy Only	6,374	86.8	73.6	−13.2** (−14.8 to −11.8)	11.8** (8.0 to 15.5)	4,366	5,840	1,474** (1,139 to 1,738)	−3,612** (−5,275 to −1,773)
Physical Health Costs	XR-NTX	211	94.3	91.0	−3.3 (−8.4 to 1.3)	----	4,309	3,249	−1,060 (−2,582 to 133)	----
	Oral NTX	1,408	92.2	88.7	−3.5** (−6.1 to −1.7)	0.2 (−5.1 to 4.6)	4,412	4,192	−220 (−910 to 352)	−840 (−2,625 to 526)
	Acamprosate	2,479	93.9	87.5	−6.4** (−8.0 to −4.9)	3.1 (−2.6 to 6.9)	4,005	4,193	188 (−321 to 608)	−1,248* (−2,829 to −95)
	Disulfiram	1,043	94.0	85.9	−8.1** (−10.4 to −5.7)	4.8 (−0.3 to 9.6)	3,798	3,672	−126 (−864 to 525)	−934 (−2,406 to 408)
	Psychosocial Therapy Only	6,374	59.9	49.7	−10.2** (−11.9 to −8.9)	6.9** (1.8 to 11.4)	3,610	3,389	−221 (−524 to 61)	−839 (−2,591 to 308)
Behavioral Health Costs	XR-NTX	211	70.1	67.8	−2.3 (−8.6 to 2.5)	----	5,677	4,070	−1,607* (−3,635 to −196)	----
	Oral NTX	1,408	58.9	56.7	−2.2* (−4.1 to −0.3)	−0.1 (−6.7 to 6.0)	5,195	4,489	−706* (−1,435 to −64)	−901 (−2,808 to 856)
	Acamprosate	2,479	61.6	56.3	−5.3** (−6.8 to −3.6)	3.0 (−3.0 to 8.3)	4,207	4,184	−23 (−431 to 435)	−1,584* (−3,661 to −168)
	Disulfiram	1,043	46.3	45.3	−1.0 (−3.2 to 1.2)	−1.3 (−7.5 to 3.3)	3,531	3,138	−393 (−976 to 198)	−1,214 (−3,220 to 363)
	Psychosocial Therapy Only	6,374	58.0	47.2	−10.8** (−12.1 to −9.5)	8.5** (3.2 to 13.7)	2,716	5,412	2,696** (2,334 to 2,978)	−4,303** (−6,349 to −2,910)

[a] The model contains all demographics (gender, age, region, beneficiary status, plan type), treatment group, time relative to index date, and the treatment*time interaction.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A3. Physical and Behavioral Health Admissions in the Full Sample[a]

Variables			Percentage of Patients with Any Admissions (%)				Average Number of Admissions Among Patients with Any Admissions			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Total Inpatient Admissions	XR-NTX	211	39.8	18.5	−21.3** (−29.8 to −13.2)	----	2.65	2.92	0.27 (−0.88 to 2.17)	----
	Oral NTX	1,408	29.5	16.5	−13.0** (−15.7 to −10.6)	−8.3* (−18.2 to -0.9)	2.13	2.47	0.34 (-0.07 to 0.90)	−0.07 (−1.40 to 1.96)
	Acamprosate	2,479	36.3	17.3	−19.0** (−21.4 to −17.2)	−2.3 (−9.8 to 5.3)	2.04	2.87	0.83** (0.41 to 1.19)	−0.56 (−1.76 to 1.25)
	Disulfiram	1,043	20.2	12.1	−8.1** (−11.2 to −5.1)	−13.2** (−22.8 to -4.9)	2.11	2.42	0.31 (−0.28 to 0.98)	−0.04 (−1.54 to 1.92)
	Psychosocial Therapy Only	6,374	28.1	15.8	−12.3** (−13.7 to −11.2)	−9.0* (−17.7 to -1.4)	1.98	3.08	1.10** (0.86 to 1.44)	−0.83 (−2.03 to 1.12)
Inpatient Physical Health Admissions	XR-NTX	211	13.7	6.6	−7.1** (−14.5 to −2.4)	----	1.36	1.31	−0.05 (−0.35 to 0.39)	----
	Oral NTX	1,408	9.9	7.3	−2.6** (−4.7 to −0.9)	−4.5 (−11.8 to 1.1)	1.47	1.66	0.19 (−0.10 to 0.50)	−0.24 (−0.67 to 0.38)
	Acamprosate	2,479	12.2	8.2	−4.0** (−5.8 to −2.6)	−3.1 (−10.0 to 2.4)	1.43	1.54	0.11 (−0.08 to 0.29)	−0.16 (−0.51 to 0.39)
	Disulfiram	1,043	8.4	5.6	−2.8** (−4.8 to −0.7)	−4.3 (−11.9 to 1.1)	1.63	1.66	0.03 (−0.37 to 0.36)	−0.08 (−0.48 to 0.49)
	Psychosocial Therapy Only	6,374	10.6	6.3	−4.3** (−5.3 to −3.3)	−2.8 (−11.4 to 2.0)	1.44	1.42	−0.02 (−0.15 to 0.07)	−0.03 (−0.38 to 0.37)
Inpatient Behavioral Health Admissions	XR-NTX	211	32.2	14.2	−18.0** (−24.7 to −11.3)	----	2.68	3.15	0.47 (−0.94 to 2.59)	----
	Oral NTX	1,408	23.7	11.6	−12.1** (−14.0 to −9.8)	−5.9 (−13.0 to 0.0)	2.02	2.49	0.47 (-0.05 to 1.29)	0.00 (−1.56 to 2.86)
	Acamprosate	2,479	29.4	12.2	−17.2** (−19.4 to −15.7)	−0.8 (−7.9 to 5.5)	1.91	3.00	1.09** (0.61 to 1.65)	−0.62 (−2.02 to 1.60)
	Disulfiram	1,043	14.1	7.7	−6.4** (−9.0 to −3.6)	−11.6** (−19.1 to −5.4)	2.07	2.49	0.42 (−0.42 to 1.49)	0.05 (−1.82 to 2.32)
	Psychosocial Therapy Only	6,374	20.6	11.1	−9.5** (−10.6 to −8.5)	−8.5** (−15.3 to −1.9)	1.93	3.53	1.60** (1.27 to 2.04)	−1.13 (−2.57 to 1.14)

[a] The model contains all demographics (gender, age, region, beneficiary status, plan type), treatment group, time relative to index date, and the treatment*time interaction.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A4. Outpatient Behavioral Health and Emergency Room (ER) Visits in the Full Sample[a]

Variables			Percentage of Patients with Any Visits (%)				Average Number of Visits Among Patients with Any Visits			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Outpatient Psychosocial Therapy Visits	XR-NTX	211	49.8	52.6	2.8 (−3.1 to 10.0)	----	5.65	7.02	1.37* (0.11 to 2.72)	----
	Oral NTX	1,408	40.8	43.3	2.5* (0.5 to 4.6)	0.03 (−6.3 to 7.3)	6.52	7.90	1.38** (0.84 to 2.04)	−0.01 (−1.45 to 1.47)
	Acamprosate	2,479	34.6	40.1	5.5** (4.0 to 7.2)	−2.7 (−10.3 to 2.8)	4.97	6.60	1.63** (1.13 to 1.99)	−0.26 (−1.71 to 0.98)
	Disulfiram	1,043	28.8	33.9	5.1** (3.1 to 7.4)	−2.3 (−8.8 to 4.0)	6.76	7.56	0.80 (−0.13 to 1.70)	0.57 (−1.06 to 2.12)
	Psychosocial Therapy Only	6,374	0.3	0.4	0.1 (−0.1 to 0.3)	2.7 (−3.2 to 9.9)	1.76	7.68	5.92** (2.70 to 9.33)	−4.55** (−8.09 to −1.12)
Outpatient Behavioral Health Hospital and Facility Visits	XR-NTX	211	34.1	32.2	−1.9 (−6.9 to 6.5)	----	8.64	12.83	4.19* (0.56 to 8.36)	----
	Oral NTX	1,408	22.9	26.6	3.7** (1.7 to 5.9)	−5.6 (−11.2 to 2.8)	9.52	14.42	4.90** (3.00 to 6.78)	−0.71 (−5.23 to 3.89)
	Acamprosate	2,479	22.3	30.0	7.7** (6.0 to 9.5)	−9.6* (−14.8 to −1.7)	6.78	13.23	6.45** (5.44 to 7.63)	−2.26 (−6.70 to 1.70)
	Disulfiram	1,043	20.1	20.9	0.8 (−1.7 to 3.7)	−2.7 (−9.6 to 5.0)	8.40	16.33	7.93** (5.97 to 10.51)	−3.74 (−8.45 to 0.34)
	Psychosocial Therapy Only	6,374	46.3	42.1	−4.2** (−5.3 to −2.9)	2.3 (−2.7 to 11.0)	3.07	15.07	12.0** (11.33 to 12.50)	−7.80** (−11.27 to −3.54)
ER Visits	XR-NTX	211	40.7	28.4	−12.3** (−19.4 to −3.9)	----	1.83	1.80	−0.03 (−0.57 to 0.59)	----
	Oral NTX	1,408	33.1	22.9	−10.2** (−12.8 to −6.9)	−2.1 (−10.7 to 6.2)	1.85	1.90	0.05 (−0.10 to 0.34)	−0.08 (−0.65 to 0.57)
	Acamprosate	2,479	35.4	23.8	−11.6** (−14.0 to −9.5)	−0.7 (−9.5 to 6.6)	1.77	1.94	0.17* (0.04 to 0.29)	−0.20 (−0.75 to 0.47)
	Disulfiram	1,043	28.7	22.5	−6.2** (−9.5 to −3.2)	−6.1 (−14.1 to 3.0)	1.69	1.65	−0.04 (−0.24 to 0.09)	0.01 (−0.50 to 0.65)
	Psychosocial Therapy Only	6,374	33.6	21.5	−12.1** (−13.3 to −10.8)	−0.2 (−8.3 to 6.9)	1.46	1.47	0.01 (−0.06 to 0.08)	−0.04 (−0.58 to 0.60)

[a] The model contains all demographics (gender, age, region, beneficiary status, plan type), treatment group, time relative to index date, and the treatment*time interaction.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A5. Physical and Behavioral Health Non-Pharmacy Costs Among Patients with Pre-Treatment Physical Health Comorbidities[a]

Variables			Percentage of Patients with Any Spending (%)				Costs Among Patients with Nonzero Spending ($)			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Total Non-Pharmacy Costs	XR-NTX	56	100.0	94.6	−5.4 (−12.5 to 0.0)	----	13,774	7,132	−6,642** (−9,826 to −3,477)	----
	Oral NTX	259	100.0	97.7	−2.3* (−4.0 to −0.8)	−3.1 (−10.6 to 2.7)	12,072	11,124	−948 (−3,717 to 2,196)	−5,694** (−10,121 to −1,704)
	Acamprosate	629	100.0	95.9	−4.1** (−6.1 to −2.6)	−1.3 (−8.8 to 4.1)	11,649	9,619	−2,030* (−3,505 to −558)	−4,612** (−7,845 to −1,140)
	Disulfiram	205	100.0	95.1	−4.9** (−8.1 to −2.3)	−0.5 (−8.5 to 5.8)	10,640	7,432	−3,208** (−5,678 to −826)	−3,434 (−7,366 to 537)
	Psychosocial Therapy Only	626	100.0	77.6	−22.4** (−25.5 to −19.5)	17.0** (8.0 to 22.7)	10,749	9,233	−1,516 (−3,191 to 177)	−5,126** (−8,732 to −1,789)
Physical Health Costs	XR-NTX	56	100.0	91.1	−8.9** (−17.9 to −2.8)	----	7,927	3,518	−4,409** (−7,104 to −1,824)	----
	Oral NTX	259	98.5	95.8	−2.7 (−5.6 to 0.0)	−6.2 (−18.1 to 0.2)	9,279	8,355	−924 (−3,976 to 1,661)	−3,485* (−7,139 to −397)
	Acamprosate	629	99.5	92.8	−6.7** (−8.8 to −4.4)	−2.2 (−11.9 to 4.3)	8,177	6,778	−1,399 (−2,626 to 29)	−3,010** (−6,535 to −550)
	Disulfiram	205	99.5	92.7	−6.8** (−10.6 to −3.0)	−2.1 (−11.5 to 4.3)	7,807	5,602	−2,205* (−4,549 to −300)	−2,204 (−5,626 to 608)
	Psychosocial Therapy Only	626	91.4	65.0	−26.4** (−29.4 to −22.2)	17.5* (7.5 to 24.4)	8,653	6,164	−2,489** (−4,179 to −1,092)	−1,920 (−5,118 to 885)
Behavioral Health Costs	XR-NTX	56	80.4	78.6	−1.8 (−17.1 to 9.7)	----	7,414	4,450	−2,964** (−5,989 to −770)	----
	Oral NTX	259	61.4	58.7	−2.7 (−8.3 to 1.9)	0.9 (−19.2 to 12.8)	4,909	5,116	207 (−1,180 to 1,455)	−3,171* (−6,521 to −49)
	Acamprosate	629	68.3	58.3	−10.0** (−13.1 to −6.6)	8.2 (−7.3 to 19.3)	5,189	5,019	−170 (−982 to 1,044)	−2,794* (−6,287 to −447)
	Disulfiram	205	55.1	45.8	−9.3** (−15.5 to −4.6)	7.5 (−15.8 to 18.8)	5,194	3,851	−1,343 (−3,263 to 41)	−1,621 (−5,198 to 1,008)
	Psychosocial Therapy Only	626	61.8	44.2	−17.6** (−20.6 to −12.6)	15.8* (0.8 to 26.8)	4,547	6,949	2,402** (1,355 to 3,684)	−5,366** (−9,066 to −2,914)

[a] The model contains all demographics, treatment group, time relative to index date, medical comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A6. Physical and Behavioral Health Admissions Among Patients with Pre-Treatment Physical Health Comorbidities[a]

Variables			Percentage of Patients with Any Admissions (%)				Average Number of Admissions Among Patients with Any Admissions			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison
Total Inpatient Admissions	XR-NTX	56	62.5	25.0	−37.5** (−54.2 to −23.5)	----	2.99	3.05	0.06 (−1.29 to 3.54)	----
	Oral NTX	259	46.3	23.5	−22.8** (−29.3 to −15.7)	−14.7 (−36.6 to 1.0)	2.14	3.31	1.17* (0.13 to 2.46)	−1.11 (−3.07 to 2.37)
	Acamprosate	629	59.5	25.6	−33.9** (−37.4 to −29.1)	−3.6 (−20.8 to 12.8)	2.18	2.86	0.68* (0.07 to 1.25)	−0.62 (−2.13 to 3.36)
	Disulfiram	205	45.4	20.5	−24.9** (−33.0 to −16.2)	−12.6 (−34.7 to 2.0)	1.91	2.50	0.59 (−0.10 to 1.58)	−0.53 (−2.25 to 2.72)
	Psychosocial Therapy Only	626	70.1	28.3	−41.8** (−46.4 to −37.4)	4.3 (−13.2 to 18.1)	2.05	2.89	0.84** (0.31 to 1.37)	−0.78 (−2.19 to 3.04)
Inpatient Physical Health Admissions	XR-NTX	56	35.7	5.3	−30.4** (−49.1 to −19.6)	----	1.56	1.66	0.10 (−0.76 to 1.65)	----
	Oral NTX	259	23.5	13.5	−10.0** (−15.4 to −3.9)	−20.4** (−38.6 to −5.9)	1.72	1.97	0.25 (−0.22 to 0.66)	−0.15 (−1.15 to 1.44)
	Acamprosate	629	31.6	13.8	−17.8** (−21.3 to −13.4)	−12.6* (−32.8 to −0.3)	1.57	1.87	0.30 (-0.01 to 0.63)	−0.20 (−1.12 to 1.79)
	Disulfiram	205	23.9	11.2	−12.7** (−19.2 to −6.8)	−17.7* (−34.6 to −4.2)	1.61	1.71	0.10 (−0.40 to 0.73)	0.00 (−1.05 to 1.79)
	Psychosocial Therapy Only	626	43.9	16.3	−27.6** (−32.3 to −23.6)	−2.8 (−21.0 to 9.1)	1.66	1.70	0.04 (−0.22 to 0.28)	0.06 (−0.80 to 1.59)
Inpatient Behavioral Health Admissions	XR-NTX	56	44.6	21.4	−23.2** (−39.0 to -10.3)	----	2.89	3.14	0.25 (−1.06 to 3.61)	----
	Oral NTX	259	31.3	14.7	−16.6** (−22.6 to -9.7)	-6.6 (−30.7 to 5.2)	1.79	3.46	1.67* (0.18 to 3.91)	−1.42 (−3.82 to 2.40)
	Acamprosate	629	42.3	17.3	−25.0** (−28.0 to −20.3)	1.8 (−17.9 to 13.9)	1.85	2.70	0.85 (0.01 to 1.66)	−0.60 (−2.01 to 2.80)
	Disulfiram	205	27.3	11.7	−15.6** (−21.6 to −9.1)	-7.6 (−32.6 to 3.6)	1.82	2.61	0.79 (−0.43 to 2.33)	−0.54 (−3.04 to 2.31)
	Psychosocial Therapy Only	626	40.5	16.1	−24.4** (−28.0 to −20.1)	1.2 (-12.5 to 15.3)	1.69	3.40	1.71** (0.91 to 2.51)	−1.46 (−3.07 to 1.54)

[a] The model contains all demographics, treatment group, time relative to index date, medical comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A7. Outpatient Behavioral Health and ER Visits Among Patients with Pre-Treatment Physical Health Comorbidities[a]

Variables			Percentage of Patients with Any Visits (%)				Average Number of Visits Among Patients with Any Visits			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Outpatient Psychosocial Therapy Visits[b]	XR-NTX	56	48.2	50.0	1.8 (−9.4 to 15.8)	----	6.86	7.79	0.93 (−2.02 to 3.82)	----
	Oral NTX	259	36.3	40.2	3.9 (-1.5 to 8.5)	−2.1 (−13.8 to 12.9)	5.19	7.43	2.24** (1.01 to 3.86)	−1.31 (−4.75 to 1.84)
	Acamprosate	629	31.0	38.5	7.5** (3.9 to 11.4)	−5.7 (−16.9 to 9.5)	4.85	6.26	1.41* (0.55 to 2.55)	−0.48 (−3.63 to 2.58)
	Disulfiram	205	27.8	32.7	4.9 (−0.9 to 10.4)	-3.1 (−16.9 to 12.5)	6.59	7.68	1.09 (−0.75 to 3.03)	−0.16 (−3.65 to 3.30)
Outpatient Behavioral Health Hospital and Facility Visits	XR-NTX	56	48.2	46.4	−1.8 (−17.9 to 15.6)	----	11.30	15.57	4.27 (−5.30 to 10.52)	----
	Oral NTX	259	22.8	30.9	8.1** (2.3 to 14.0)	−9.9 (−26.6 to 7.9)	8.30	14.82	6.52** (3.21 to 9.91)	−2.25 (−10.75 to 4.67)
	Acamprosate	629	24.0	32.8	8.8** (5.2 to 12.0)	−10.6 (−25.9 to 7.9)	7.19	14.07	6.88** (5.12 to 8.85)	−2.61 (−11.60 to 3.70)
	Disulfiram	205	25.9	23.9	−2.0 (−8.5 to 4.2)	0.2 (−19.8 to 16.6)	8.40	17.06	8.66** (2.74 to 13.69)	−4.39 (−13.64 to 2.93)
	Psychosocial Therapy Only	626	37.5	37.5	0.0 (−3.5 to 3.9)	−1.8 (−18.3 to 14.9)	4.28	15.16	10.88** (8.52 to 12.86)	−6.61* (−16.18 to −0.48)
ER Visits	XR-NTX	56	69.6	33.9	−35.7** (−52.8 to −19.0)	----	2.31	1.87	−0.44 (−1.42 to 0.64)	----
	Oral NTX	259	50.2	29.0	−21.2** (−27.6 to −14.9)	−14.5 (−29.7 to 3.3)	1.99	2.49	0.50* (0.11 to 1.35)	−0.94 (−2.17 to 0.21)
	Acamprosate	629	55.5	32.0	−23.5** (−27.5 to −17.9)	−12.2 (−30.3 to 5.0)	2.04	2.31	0.27 (0.00 to 0.61)	−0.71 (−1.84 to 0.33)
	Disulfiram	205	51.7	32.2	−19.5** (−26.3 to −11.2)	−16.2 (−33.9 to 1.2)	2.00	1.84	−0.16 (−0.56 to 0.15)	−0.28 (−1.26 to 0.84)
	Psychosocial Therapy Only	626	48.4	27.3	−21.1** (−25.6 to −16.5)	−14.6 (−31.8 to 3.4)	1.81	1.67	−0.14 (−0.35 to 0.07)	−0.30 (−1.33 to 0.81)

[a] The model contains all demographics, treatment group, time relative to index date, medical comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities.

[b] There were no patients with any outpatient psychosocial therapy visits in the Psychosocial Therapy Only group

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A8. Physical and Behavioral Health Costs Among Patients with Pre-Treatment Mental Health Comorbidities[a]

Variables			Percentage of Patients with Any Spending (%)				Costs Among Patients with Nonzero Spending ($)			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Total Non-Pharmacy Costs	XR-NTX	86	100.0	96.5	−3.5* (−8.8 to −1.1)	----	11,486	6,967	−4,519** (−7,370 to −1,187)	----
	Oral NTX	574	100.0	95.3	−4.7** (−6.6 to −3.4)	1.2 (−3.8 to 4.2)	9,355	9,236	−119 (−1,427 to 1,334)	−4,400** (−7,699 to −929)
	Acamprosate	939	100.0	97.0	−3.0** (−4.1 to −1.8)	−0.5 (−5.9 to 2.5)	8,065	7,556	−509 (−1,433 to 529)	−4,010** (−7,068 to −845)
	Disulfiram	321	100.0	95.0	−5.0** (−7.9 to −3.1)	1.5 (−4.8 to 5.5)	8,357	6,592	−1,765 (−3,506 to 257)	−2,754 (−5,963 to 472)
	Psychosocial Therapy Only	457	100.0	77.2	−22.8** (−26.9 to −18.7)	19.3** (12.2 to 23.8)	10,808	9,218	−1,590 (−3,161 to 107)	−2,929 (−6,541 to 1,044)
Physical Health Costs	XR-NTX	86	95.3	89.5	−5.8 (−13.3 to 1.1)	----	5,676	3,654	−2,022* (−3,912 to −5)	----
	Oral NTX	574	92.7	89.9	−2.8* (−5.8 to −0.2)	−3.0 (−10.6 to 6.1)	4,809	5,310	501 (−698 to 1,713)	−2,523* (−5,093 to −111)
	Acamprosate	939	93.9	89.5	−4.4** (−6.6 to −2.4)	−1.4 (−9.0 to 6.8)	4,571	4,551	−20 (−797 to 628)	−2,002 (−3,968 to 291)
	Disulfiram	321	95.6	87.2	−8.4** (−12.6 to −4.9)	2.6 (−6.5 to 12.3)	4,941	4,101	−840 (−2,431 to 393)	−1,182 (−3,424 to 1,571)
	Psychosocial Therapy Only	457	80.8	54.5	−26.3** (−32.2 to −21.1)	20.5** (11.4 to 30.3)	5,006	4,195	−811 (−2,027 to 256)	−1,211 (−3,546 to 1,178)
Behavioral Health Costs	XR-NTX	86	96.5	89.5	−7.0 (−13.9 to 0.0)	----	6,553	3,825	−2,728* (−4,494 to −467)	----
	Oral NTX	574	88.7	79.6	−9.1** (−11.8 to −7.0)	2.1 (−6.4 to 9.1)	5,455	4,839	−616 (−1,520 to 310)	−2,112 (−4,219 to 331)
	Acamprosate	939	90.1	79.4	−10.7** (−13.0 to −8.2)	3.7 (−4.4 to 11.2)	4,235	4,035	−200 (−727 to 412)	−2,528* (−4,706 to −654)
	Disulfiram	321	84.1	76.3	−7.8** (−12.4 to −3.0)	0.8 (−7.3 to 8.6)	4,394	3,629	−765 (−1,831 to 191)	−1,963 (−4,015 to 472)
	Psychosocial Therapy Only	457	90.1	57.5	−32.6** (−37.5 to −28.6)	25.6** (16.7 to 33.1)	7,437	8,061	624 (−585 to 2,236)	−3,352** (−5,670 to −1,104)

[a] The model contains all demographics, treatment group, time relative to index date, mental health comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities. Mental health comorbidities include schizophrenia, bipolar disorder, major depression, and anxiety.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A9. Physical and Behavioral Admissions Among Patients with Pre-Treatment Mental Health Comorbidities[a]

Variables			Percentage of Patients with Any Admissions (%)				Average Number of Admissions Among Patients with Any Admissions			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Total Inpatient Admissions	XR-NTX	86	54.6	17.4	−37.2** (−48.9 to −24.1)	----	2.60	5.05	2.45 (−0.70 to 7.59)	----
	Oral NTX	574	40.6	22.5	−18.1** (−22.5 to −14.3)	−19.1** (−32.3 to −5.6)	2.04	2.77	0.73* (0.13 to 1.76)	1.72 (−1.26 to 7.28)
	Acamprosate	939	42.5	19.0	−23.5** (−27.1 to −20.1)	−13.7 (−25.9 to 0.1)	2.39	3.05	0.66* (0.09 to 1.33)	1.79 (−1.45 to 6.91)
	Disulfiram	321	33.0	19.0	−14.0** (−20.1 to −8.1)	−23.2** (−38.5 to −10.2)	2.37	2.71	0.34 (−0.62 to 1.57)	2.11 (−1.35 to 6.70)
	Psychosocial Therapy Only	457	75.7	24.9	−50.8** (−55.1 to −45.5)	13.6* (0.8 to 28.3)	2.18	3.58	1.40** (0.43 to 2.21)	1.05 (−2.10 to 6.33)
Inpatient Physical Health Admissions	XR-NTX	86	17.4	9.3	−8.1 (−18.1 to 1.3)	----	1.48	1.34	−0.14 (−0.63 to 0.48)	----
	Oral NTX	574	12.7	9.7	−3.0 (−6.7 to 0.0)	−5.1 (−16.3 to 4.9)	1.46	1.89	0.43* (0.03 to 0.99)	−0.57 (−1.25 to 0.25)
	Acamprosate	939	13.6	8.4	−5.2** (−7.7 to −2.4)	−2.9 (−13.8 to 7.4)	1.45	1.54	0.09 (−0.15 to 0.33)	−0.23 (−0.78 to 0.54)
	Disulfiram	321	11.8	6.5	−5.3* (−9.6 to −1.3)	−2.8 (−13.3 to 7.9)	1.89	1.54	−0.35 (−1.06 to 0.21)	0.21 (−0.45 to 1.12)
	Psychosocial Therapy Only	457	19.3	7.0	−12.3** (−16.5 to −8.8)	4.2 (−6.0 to 14.9)	1.47	1.69	0.22 (−0.21 to 0.60)	−0.36 (−0.95 to 0.61)
Inpatient Behavioral Health Admissions	XR-NTX	86	47.7	12.8	−34.9** (−46.8 to −22.5)	----	2.42	5.86	3.44 (−0.38 to 9.43)	----
	Oral NTX	574	35.0	16.9	−18.1** (−22.3 to −13.5)	−16.8** (−30.0 to −4.3)	1.83	2.61	0.78* (0.10 to 2.13)	2.66 (−1.18 to 8.77)
	Acamprosate	939	37.8	14.7	−23.1** (−26.6 to −20.2)	−11.8 (−24.3 to 1.3)	2.15	3.03	0.88* (0.19 to 1.56)	2.56 (−1.20 to 8.65)
	Disulfiram	321	26.5	15.0	−11.5** (−16.8 to −5.3)	−23.4** (−37.3 to −10.4)	2.13	2.75	0.62 (−0.67 to 2.09)	2.82 (−1.19 to 8.64)
	Psychosocial Therapy Only	457	71.6	22.1	−49.5** (−54.8 to −44.2)	14.6 (−0.3 to 25.7)	1.92	3.52	1.60** (0.57 to 2.52)	1.84 (−1.88 to 7.82)

[a] The model contains all demographics, treatment group, time relative to index date, mental health comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities. Mental health comorbidities include schizophrenia, bipolar disorder, major depression, and anxiety.

* $0.01 \leq p < 0.05$

** $p < 0.01$

Table A10. Outpatient Behavioral Health and ER Visits Among Patients with Pre-Treatment Mental Health Comorbidities[a]

Variables			Percentage of Patients with Any Visits (%)				Average Number of Visits Among Patients with Any Visits			
Outcome	Treatment Group	N	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)	Pre-Treatment	Post-Treatment	Change (95% CI)	Change in XR-NTX Relative to Comparison Group (95% CI)
Outpatient Psychosocial Therapy Visits[b]	XR-NTX	86	77.9	75.6	−2.3 (−10.7 to −8.1)	----	6.27	7.38	1.11 (−0.45 to 4.06)	----
	Oral NTX	574	72.3	66.7	−5.6* (−8.7 to −1.9)	3.3 (−6.9 to 13.7)	7.17	8.78	1.61** (0.87 to 2.23)	−0.50 (−2.16 to 2.53)
	Acamprosate	939	66.3	65.7	−0.6 (−3.5 to 2.0)	−1.7 (−10.2 to 9.5)	5.58	7.16	1.58** (1.06 to 2.03)	−0.47 (−2.29 to 2.27)
	Disulfiram	321	67.9	66.3	−1.6 (−5.8 to 2.6)	−0.7 (−10.3 to 9.3)	7.69	8.83	1.14* (0.05 to 2.24)	−0.03 (−2.14 to 2.88)
Outpatient Behavioral Health Hospital and Facility Visits	XR-NTX	86	52.3	40.7	−11.6** (−23.3 to -1.1)	----	8.31	15.01	6.70** (1.40 to 13.11)	----
	Oral NTX	574	31.7	36.1	4.4** (1.2 to 7.8)	−16.0** (−28.9 to −4.5)	9.28	14.02	4.74** (2.65 to 6.91)	1.96 (−4.60 to 8.31)
	Acamprosate	939	31.4	38.1	6.7** (4.0 to 10.4)	−18.3** (−30.6 to −7.2)	6.79	12.47	5.68** (4.41 to 7.48)	1.02 (−5.23 to 7.44)
	Disulfiram	321	30.5	32.4	1.9 (−3.9 to 7.8)	−13.5** (−28.3 to −2.1)	9.78	13.71	3.93** (1.14 to 6.78)	2.77 (−3.29 to 8.84)
	Psychosocial Therapy Only	457	58.8	49.2	−9.6** (−14.7 to −5.2)	−2.0 (-14.9 to 9.3)	6.84	14.51	7.67** (5.11 to 10.15)	-0.97 (−7.33 to 5.73)
ER Visits	XR-NTX	86	57.0	31.4	−25.6** (−41.8 to −13.9)	----	2.04	2.16	0.12 (−0.68 to 1.24)	----
	Oral NTX	574	42.5	28.6	−13.9** (−17.9 to −8.8)	−11.6 (−30.5 to 1.3)	2.09	2.10	0.01 (-0.22 to 0.44)	0.11 (−0.95 to 1.22)
	Acamprosate	939	45.3	28.4	−16.9** (−20.4 to −13.3)	−8.7 (−25.4 to 4.7)	1.97	2.01	0.04 (-0.17 to 0.24)	0.08 (−0.81 to 1.15)
	Disulfiram	321	37.7	29.6	−8.1** (−14.6 to −2.6)	−17.5** (−37.1 to −4.0)	2.06	1.95	-0.11 (−0.49 to 0.21)	0.23 (−0.68 to 1.42)
	Psychosocial Therapy Only	457	61.9	30.9	−31.0** (−36.2 to −25.8)	5.4 (−11.4 to 20.3)	1.88	1.60	-0.28* (-0.52 to -0.03)	0.40 (−0.49 to 1.67)

[a] The model contains all demographics, treatment group, time relative to index date, mental health comorbidities (yes/no), and the following interactions: treatment*time, treatment*comorbidities, time*comorbidities, and treatment*time*comorbidities. Mental health comorbidities include schizophrenia, bipolar disorder, major depression, and anxiety.

[b] There were too few psychosocial therapy only patients with any psychosocial therapy visits in the mental health comorbidities subset (n = 7) to include them in the model.

* $0.01 \leq p < 0.05$

** $p < 0.01$