Cost and Utilization Outcomes of Opioid-Dependence Treatments

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Abstract

Objectives: To evaluate the healthcare costs associated with treatment of opioid-dependence disorder with medications versus no medication, and with the 4 agents approved by the US Food and Drug Administration (FDA).

Study Design: Retrospective claims database analysis.

Methods: Eligible adults with opioid dependence were identified from a large US health plan and the PharMetrics Integrated Database. Data included all medical and pharmacy claims at all available healthcare sites. Case-mix adjustment was applied using baseline demographic, clinical, and healthcare utilization variables for 13,316 patients; half of these patients used an FDA-approved medication for opioid dependence. A similar comparison was performed among 10,513 patients treated with extended-release naltrexone (NTX-XR) (n = 156) prior to FDA approval for opioid dependence or with a medication approved at the time: oral naltrexone (NTX) (n = 845), buprenorphine (n = 7596), or methadone (n = 1916). Analyses calculated 6-month persistence, utilization, and paid claims for opioid-dependence medications, detoxification and rehabilitation, opioid-related and non-related inpatient admissions, outpatient services, and total costs.

Results: Medication was associated with fewer inpatient admissions of all types. Despite higher costs for medications, total healthcare costs, including inpatient, outpatient, and pharmacy costs, were 29% lower for patients who received a medication for opioid dependence versus patients treated without medication. Patients given XR-NTX had fewer opioid-related and non–opioid-related hospitalizations than patients receiving oral medications. Despite higher costs for XR-NTX, total healthcare costs were not significantly different from those for oral NTX or buprenorphine, and were 49% lower than those for methadone.

Conclusion: Patients with opioid dependence who received medication for this disorder had lower hospital utilization and total costs than patients who did not receive pharmacologic therapy. Patients who received XR-NTX had lower inpatient healthcare utilization at comparable or lower total costs than those receiving oral medications.

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For author information and disclosures, see end of text.

Opioid-dependence disorder, or addiction, is a complex brain disease characterized by "uncontrollable drug craving, along with compulsive drug seeking and use that persist even in the face of devastating consequences."[1] In 2009, there were over 2 million opioid-dependent adults in the United States[2] and prescription opioid dependence has been increasing over the last 20 years due to growth in prescribing of high potency opioids for the treatment of pain. Drug overdose deaths now surpass gunshot deaths; in 16 states overdose deaths are more common than lethal car crashes, and drugged driving occurs at higher levels than alcohol-impaired driving.[3] Among those dependent upon heroin, it is estimated that more than 18 years of potential life are lost by age 65, with the leading causes of death being overdose, chronic liver disease, and accidents.[4] The cost of heroin dependence in the United States was estimated at $21 billion in 2000.[5]

There are 3 main classes of oral pharmacologic treatments for opioid dependence: opioid receptor agonists (methadone),[6] partial agonists (buprenorphine, buprenorphine/naloxone),[7] and antagonists (oral naltrexone [NTX]).[8] Agonist therapy is effective for a broad range of dependence consequences and outcomes, although diversion and abuse can be problematic.[9] Antagonist therapy (ie, oral NTX) is not abused; however, its clinical effectiveness has been limited by poor patient compliance with daily dosing,[10] leading the National Institute on Drug Abuse to call for a sustained-release antagonist preparation.[11] Extended-release naltrexone (XR-NTX)[12] was approved by the US Food and Drug Administration (FDA) in October 2010 for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following detoxification.

Much of the population with opioid dependence remains untreated, due to obstacles including denial about the disease, poor motivation, stigma, limited insurance coverage, and limited access to care; factors that have been proposed to improve this situation include expanded access to opioid agonist treatment, treatment with a nonreinforcing "blocker," treatment in a conventional medical setting, and an approach that conforms to the abstinence model.[3,13-16]

Given the growing health and social burdens of opioid dependence and new formulations and approaches to treatment introduced in the past 10 years, the present study was designed to examine a comprehensive range of real-world healthcare costs and

utilization with available treatments, including treatment with no medication, treatment with any of the currently approved medications, and among the currently approved medications, treatment with each of the 4 agents.

Methods

Data Sources and Study Population

Health Insurance Portability and Accountability Act–compliant pharmacy and medical administrative claims data from a proprietary US health plan and the PharMetrics Integrated Database for calendar years 2005 through 2009 were used for this retrospective, longitudinal study. For the first source, data for approximately 14 million individuals was available in 2008. The PharMetrics Integrated Database includes 85 US health plans providing healthcare coverage to more than 10 million persons annually throughout the United States. These data sources are well validated and were chosen because they cover large numbers of patients across all parts of the United States.

The end points of the study were healthcare cost and utilization. Two different comparisons were conducted: (1) between treated patients with any medication versus no medication, and (2) among patients treated with medication, comparison of patients treated with (a) XR-NTX; (b) oral NTX; (c) buprenorphine (with or without naloxone); and (d) methadone. Patients treated with XR-NTX were identified on the basis of an outpatient drug claim from the National Drug Code (NDC) or medical claims from the Healthcare Common Procedure Coding System code (because it is the 1 agent administered with a procedure). The other medications were identified using outpatient drug claims based on NDCs.

For patients in the no medication group, the index date was defined as the first medical claim for a nonpharmacologic treatment, such as a detoxification facility claim, a substance abuse treatment facility claim, or a substance abuse counseling claim. The index date for the group with medication use was determined as the earliest pharmacy claim for opioid medication.

The database's study population included patients continuously enrolled in a commercial health plan for at least 1 year (6 months pre–index date and 6 months post–index date). Patients were required to have at least 1 claim for opioid dependence or opioid-use disorder (*International Classification of Diseases, 9th Revision, Clinical Modification* [*ICD-9-CM*] codes 304.0x, 304.7x) in the 6 months prior to the index date or on the index date. Patients were excluded from the analysis if they (1) had claims for pharmacologic treatment for opioid dependence in the 1 month prior to the index date for patients with claims for oral NTX, buprenorphine, methadone, or nonpharmacologic treatment on the index date; or (2) had claims with a diagnosis of acute hepatitis or liver failure in the 6 months pre-index. This later restriction was applied due to the varying hepatic safety profiles of the medications.[17-19] **Figure 1** details the patient cohorts.

Study Variables

Patients' age, sex, and geographic region were determined from the claims record. Using a previously validated formula for socioeconomic status,[20] we constructed a summary measure of socioeconomic status for each US Zone Improvement Plan (ZIP) code using data on income, education, and occupation from the 2000 US Census, and then linked this information to the patients' ZIP code of residence in the analytic files.[21] Comorbid conditions were measured during the 6-month period before the index date and defined using the methods of Elixhauser[22] and Charlson[23] to produce a single score for use in multivariate models. The Deyo-Charlson comorbidity score is an *ICD-9* code adaption of the Charlson index, which assigns a range of weights, from 1 to 6 according to disease severity, for 19 conditions. The Elixhauser score is also a claims-based comorbidity index which sums a patient's comorbid conditions from among 30 *ICD-9-CM* comorbidity flags, differentiating secondary diagnoses from comorbidities by using diagnosis-related groups.

Costs were calculated using the actual patient claims for healthcare use in the matched cohort. They are measured during both the pre- and post-index periods. In addition to the overall costs, the costs of detoxification and/or rehabilitation visits, opioid- and non–opioid-related inpatient and outpatient visits and emergency department (ED) visits, opioid-related physician visits, and opioid and substance abuse psychosocial provider visits were calculated.

Healthcare utilizations are represented per 1000 patients and detailed similar to healthcare costs. Adherence and persistence were measured using medication possession ratio (MPR) and time from the index date until time of discontinuation. MPR was calculated as the ratio of days' supply of the index medication to total days in the observation period and it was corrected for inpatient events under the assumption that during hospitalization, medication is supplied by the facility. The date of discontinuation was defined by the run-out days supply of the last prescription filled prior to the gap in therapy.

Analyses

Baseline characteristics were compared between patient cohorts and descriptive statistics were calculated as mean

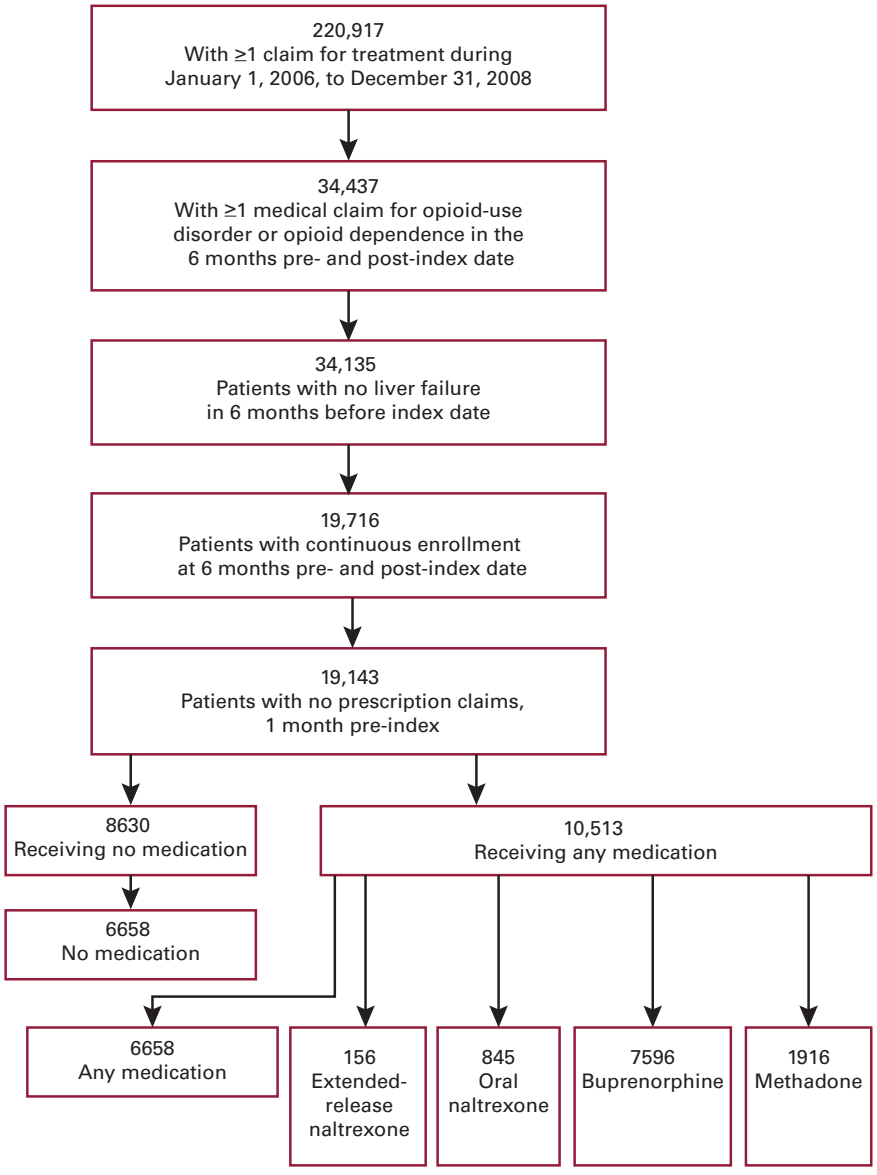
(standard deviation) and percentages. Differences between the cohorts were analyzed using the *t*-test, Mann-Whitney U tests, and χ^2 tests.

A challenge to retrospective cohort studies in general—and to this study in particular—is the question of comparability of patient groups at the time of treatment initiation (ie, is the physician equally likely to choose between the treatment options, or rather is the choice of treatment based on patient profile?). Differences in patient and provider characteristics that influence choice of treatment can confound healthcare utilization and costs, especially when one of the treatments is used off label. One method to adjust for differences in patient profiles is propensity-score analysis.[24-26] Heckman et al argued convincingly that if patients are matched using the propensity score, up to 85% of the bias resulting from unequal distributions in patient characteristics can be removed.[27]

Propensity-score analysis can be implemented in a variety of ways. For medication and nonmedication cohorts we used a logistic regression model to predict the probability that patients belong in each group on the basis of their observed characteristics. The model covariates consisted of age, sex, region, and socioeconomic status variables, baseline healthcare comorbidities, utilization, and costs.

Once each patient was assigned a propensity score, patients in the medication cohort were matched with the pool of patients in the nonmedication cohort. Matching was undertaken using nearest neighbor 1:1 matching and the resulting matched cohort was compared to determine whether balanced cohorts were created.[28] Statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, North Carolina) and STATA v10 (Stata Corp, College Station, Texas).

Figure 1. Patient Selection Process



For treatment types in the medication cohort, to further control for unobserved biases, the instrumental variable (IV) approach was used. One of the limitations of propensity-score matching analyses is that they control for observed bias (ie, selection from observed and measured factors) but not for unobserved bias. The IV approach is a technique that can be used to control for both observed and unobserved sources of bias, and to ascertain whether the results from the more standard approaches (propensity-score matching or multivariate regression) diverge from the IV results.

An instrument is a variable that does not belong in the explanatory equation and is correlated with the endogenous

Table 1. Baseline Characteristics of Opioid-Dependent Patients With and Without Any Medication

Post-Index Period (6 months after index date)	Opioid-Dependence Treatment: Any Medication (N = 10,513)	Opioid-Dependence Treatment: No Medication (N = 8630)	
Continuous variables	**Mean (SD)**	**Mean (SD)**	***P***
Pre-index Deyo-Charlson comorbidity score	0.35 (0.98)	0.33 (0.95)	.1489
Pre-index Elixhauser comorbid conditions	1.56 (1.65)	1.27 (1.61)	**<.0001**
Pre-index number of distinct psychiatric diagnoses	2.56 (1.78)	2.25 (1.85)	**<.0001**
Pre-index number of distinct psychiatric medications	2.25 (2.04)	1.61 (1.90)	**<.0001**
Healthcare utilization			
Pre-index number of detoxification facility days (number of days/1000 patients)	1092 (3110)	109 (1786)	**<.0001**
Pre-index inpatient (number of admissions/1000 patients)			
Detoxification and/or rehabilitation	195 (462)	16 (201)	**<.0001**
Opioid-related inpatient admission	221 (523)	48 (255)	**<.0001**
Non–opioid-related inpatient admission	384 (884)	277 (811)	**<.0001**
Pre-index outpatient (number of visits/1000 patients)			
Emergency department visits	1410 (4241)	1107 (3491)	**<.0001**
Opioid-related and physician provider	266 (1795)	105 (1080)	**<.0001**
Opioid-related and substance abuse psychosocial provider	117 (1154)	93 (1184)	.1471
Non–opioid-related outpatient	14,152 (16,098)	12,951 (15,279)	**<.0001**
Costs (per patient)			
Pre-index inpatient			
Cost of detoxification and/or rehabilitation	$430 ($1497)	$0 ($0)	**<.0001**
Cost of opioid-related inpatient admission	$665 ($2768)	$156 ($1513)	**<.0001**
Cost of non–opioid-related inpatient admission	$4581 ($29,587)	$2689 ($16,097)	**<.0001**
Pre-index outpatient			
Cost of emergency department visits	$4450 ($1484)	$328 ($1326)	**<.0001**
Cost of opioid-related and physician provider	$28 ($292)	$9 ($202)	**<.0001**
Cost of opioid-related and substance abuse psychosocial provider	$14 ($175)	$6 ($116)	**.0002**
Cost of non–opioid-related	$30 ($42)	$26 ($35)	**<.0001**
Pre-index pharmacy	**Mean (SD)**	**Mean (SD)**	***P***
Cost of FDA-approved opioid-dependence medications	$2 ($53)	$0 ($0)	**<.0001**
Cost of other psychiatric medications	$176 ($531)	$77 ($366)	**<.0001**
Cost of nonpsychiatric medications	$913 ($2757)	$380 ($1865)	**<.0001**
Total cost (including inpatient, outpatient, and pharmacy)	**$10,710 ($34,138)**	**$6791 ($18,916)**	**<.0001**

FDA indicates US Food and Drug Administration.

explanatory variables, conditional on the other covariates. In this study, because XR-NTX was not yet approved for the opioid dependence treatment indication (and was therefore being utilized off label), its use often required unique physician considerations and reimbursement processes resulting in unique cohort characteristics. Therefore, due to a high probability that unobserved bias would play a role in the use of this agent, copayment and physician/provider prescribing patterns derived from the claims and provider-level data served as instruments. The variables were tested to determine whether they were strong or weak instruments. From prior experience, it is known that physicians' prescribing patterns are very strong instruments because they are strongly related to treatment choices.

Results

Table 1 reports the baseline demographic and clinical characteristics of the sample, stratified by the any medication and no medication groups. Patients were similar in terms of age (36.2 years vs 36.2, respectively; *P* = NS) and sex (61.5% male vs 60.3%, respectively; *P* = NS). Patients in the any medication cohort were less likely to be from the South

Table 2. Risk-Adjusted Outcomes in Opioid-Dependent Patients With and Without Any Medication

Post-index period (6 months after index date)	Opioid-Dependence Treatment: Any Medication (N = 6658)	Opioid-Dependence Treatment: No Medication (N = 6658)	
Outcome	**Mean (SD)**	**Mean (SD)**	***P***
Post-index number of distinct psychiatric diagnoses	3.01 (1.70)	3.81 (2.14)	**<.0001**
Post-index number of distinct psychiatric medications	2.49 (2.14)	1.91 (2.05)	**<.0001**
Healthcare utilization			
Post-index number of detoxification facility days (number of days/1000 patients)	447 (2250)	4758 (7840)	**<.0001**
Post-index inpatient (number of admissions/1000 patients)			
Detoxification and/or rehabilitation	74 (317)	770 (721)	**<.0001**
Opioid-related inpatient admission	111 (407)	677 (811)	**<.0001**
Non–opioid-related inpatient admission	292 (787)	731 (1417)	**<.0001**
Post-index outpatient (number of visits/1000 patients)			
Emergency department visits	1084 (3090)	1041 (3125)	**.0372**
Opioid-related and physician provider	1104 (3941)	776 (3724)	**<.0001**
Opioid-related and substance abuse psychosocial provider	301 (2054)	553 (3196)	**<.0001**
Non–opioid-related outpatient	17,389 (17,147)	17,119 (17,663)	.1185
Costs (per patient)			
Post-index inpatient			
Cost of detoxification and/or rehabilitation	$205 ($1240)	$2083 ($3434)	**<.0001**
Cost of opioid-related inpatient admission	$381 ($2299)	$1823 ($4800)	**<.0001**
Cost of non–opioid-related inpatient admission	$2928 ($15,420)	$4184 ($21,621)	**<.0001**
Post-index outpatient			
Cost of emergency department visit	$357 ($1211)	$288 ($1182)	**<.0001**
Cost of opioid-related and physician provider	$115 ($565)	$91 ($550)	**<.0001**
Cost of opioid-related substance abuse psychosocial provider	$25 ($213)	$47 ($361)	**<.0001**
Cost of non–opioid-related	$35 ($40)	$323 ($40)	**.0002**
Post-index pharmacy			
Cost of FDA-approved opioid-dependence medications	$1078 ($1256)	$1 ($41)	**<.0001**
Cost of other psychiatric medications	$278 ($755)	$132 ($498)	**<.0001**
Cost of nonpsychiatric medications	$851 ($2158)	$357 ($1169)	**<.0001**
Total cost per patient (including inpatient, outpatient, and pharmacy)	$10,192 ($19,472)	$14,353 ($25,780)	**<.0001**

FDA indicates US Food and Drug Administration.

(18.5%) than patients in the no medication cohort (33.4%; *P* <.0001), and a smaller percentage had socioeconomic status scores in the bottom third (27.6%) relative to patients in the no medication cohort (39.8%; *P* <.0001).

As expected, given the possibilities for adverse selection, patients in the any medication cohort appeared to be sicker than those in the no medication cohort, both medically, with more having an Elixhauser comorbidity score of 3 or greater (22.9% vs 18.4%, respectively; *P* <.0001), and psychiatrically, with more having psychiatric diagnoses and taking psychiatric medications (*P* <.001 for all comparisons).

In terms of healthcare utilization, the 6 month pre-index utilization was higher in the any medication group, including number of detoxification facility days, detoxification and/or rehabilitation admissions, opioid-related and non–opioid-related inpatient and outpatient admissions, ED visits, and opioid-related provider visits.

This greater utilization in the any medication group translated into higher healthcare costs relative to the no medication group. Compared with patients not receiving medication, all of the inpatient and outpatient costs were significantly higher in those receiving medication. The

Table 3. Baseline Characteristics in Opioid-Dependent Patients by Pharmacotherapy

Pre-Index Period	Opioid Dependence Medication						
	XR-NTX (n = 156)	Oral NTX (n = 845)		Buprenorphine (n = 7596)		Methadone (n = 1916)	
Patient characteristics	**n (%)**	**n (%)**	***P***	**n (%)**	***P***	**n (%)**	***P***
Pre-index severity (Elixhauser ≥3)	53 (34.0%)	293 (34.7%)	.8658	1421 (18.1%)	**<.0001**	635 (33.1%)	.8319
Continuous variables	**Mean**	**Mean**	***P***	**Mean**	***P***	**Mean**	***P***
Clinical characteristics							
Pre-index Deyo-Charlson comorbidity score	0.22 (0.67)	0.24 (0.66)	.7494	0.26 (0.79)	.4480	0.77 (1.55)	**<.0001**
Pre-index Elixhauser comorbid conditions	2.06 (1.75)	2.05 (1.67)	.9304	1.37 (1.49)	**<.0001**	2.05 (2.04)	.9105
Pre-index number of distinct psychiatric diagnoses	3.76 (2.06)	3.78 (2.29)	.8825	2.48 (1.67)	**<.0001**	2.23 (1.69)	**<.0001**
Pre-index number of distinct psychiatric medications	2.70 (2.72)	2.48 (2.27)	.3518	2.12 (1.90)	**.0086**	2.62 (2.31)	.7277
Healthcare utilization							
Pre-index number of detoxification facility days (number of days/1000 patients)	2391 (5486)	1782 (3474)	.1828	1188 (3201)	**.0071**	301 (1918)	**<.0001**
Pre-index inpatient (number of admissions/1000 patients)							
Detoxification and/or rehabilitation	353 (660)	336 (568)	.7705	212 (475)	**.0091**	53 (261)	**<.0001**
Opioid-related inpatient admission	282 (1418)	351 (583)	.5478	237 (509)	.6913	95 (368)	.1023
Non–opioid-related inpatient admission	718 (1135)	680 (1077)	.7029	273 (717)	**<.0001**	668 (1208)	.5999
Outpatient (number of visits/1000 patients)							
Emergency department visits	1154 (2717)	1322 (3701)	.5055	1331 (3543)	.4240	1781 (6489)	**.0177**
Opioid-related and physician provider	750 (3753)	328 (1926)	.1718	284 (1844)	.1239	127 (1181)	**.0405**
Opioid-related and substance abuse psychosocial provider	699 (3880)	214 (1382)	.1250	113 (1109)	.0616	43 (576)	**.0366**
Non–opioid-related outpatient	15,494 (14,515)	14,669 (15,263)	.5184	12,125 (14,390)	**.0047**	21,853 (20,137)	**<.0001**
Costs (per patient)							
Pre-index inpatient							
Cost of detoxification and/or rehabilitation	$1083 ($2793)	$767 ($1832)	.1754	$458 ($1538)	**.0060**	$119 ($790)	**<.0001**
Cost of opioid-related inpatient admission	$607 ($1994)	$1108 ($3188)	**.0102**	$721 ($2946)	.4859	$253 ($1598)	**.0320**
Cost of non–opioid-related inpatient admission	$3407 ($7753)	$4386 ($13,666)	.2096	$2412 ($11,495)	.1189	$13,360 ($64,017)	**<.0001**
Pre-index outpatient							
Cost of emergency department visits	$425 ($1316)	$455 ($1639)	.8049	$445 ($1321)	.8502	$467 ($1961)	.7180
Cost of opioid-related and physician provider	$111 ($627)	$50 ($445)	.2449	$29 ($292)	.1047	$8 ($98)	**.0431**
Cost of opioid-related and substance abuse psychosocial provider	$74 ($567)	$41 ($311)	.4695	$13 ($156)	.1762	$4 ($53)	.1212
Cost of non–opioid-related	$30 ($34)	$29 ($35)	.9012	$26 ($37)	.1353	$48 ($56)	**<.0001**
Pre-index pharmacy							
Cost of FDA-approved opioid -dependence medications	$157 ($408)	$0 ($0)	**<.0001**	$0 ($0)	**<.0001**	$0 ($0)	**<.0001**
Cost of other psychiatric medications	$282 ($722)	$217 ($600)	.2911	$172 ($520)	.0604	$164 ($521)	**.0473**
Cost of nonpsychiatric medications	$598 ($1285)	$530 ($1295)	.5459	$845 ($2330)	**.0213**	$1377 ($4362)	**<.0001**
Total cost (including inpatient, outpatient, and pharmacy)	$10,393 ($12,677)	$11,527 ($17,455)	.3368	$7,753,216 ($15,868,760)	**.0114**	$22,098 ($71,320)	**<.0001**

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

6-month total cost including inpatient, outpatient, and pharmacy costs was $10,710 per patient in the any medication group compared with $6791 per patient in the no medication group.

Using propensity-score matching, 6658 patients from each group were matched. **Table 2** presents the risk-adjusted 6-month outcomes following the index treatment for patients in the any medication and no medication groups. Patients in the any medication group had fewer psychiatric diagnoses (3.01 vs 3.81), but more frequent use of distinct psychiatric medications (2.49 vs 1.91) relative to patients in the no medication group. Compared with patients in the no medication group, the number of detoxification facility days was significantly lower for patients in the any medication group (4758 vs 447 per 1000 patients). Post-index detoxification and/or rehabilitation admissions (74 vs 770) and opioid-related (111 vs 677) and non–opioid-related (292 vs 731) admissions were significantly lower per 1000 patients in the any medication group compared with the no medication group. Fewer inpatient admissions translated into lower inpatient costs in the any medication group. In particular, the 6-month costs per patient among those receiving medication for detoxification and/or rehabilitation admissions ($205 vs $2083) and opioid-related ($381 vs $1823) and non–opioid-related ($2928 vs $4184) admissions were significantly lower compared with those not receiving medication.

The pattern of healthcare utilization and cost for outpatient services was more mixed, with significantly higher use and cost associated with some categories of outpatient services in the any medication group. Overall healthcare cost savings, however, were $4161 per patient treated with medication relative to those not receiving medication ($10,192 vs $14,353).

Out of 10,513 patients who were given medication, 156 (1.5%) patients were treated with XR-NTX, 845 (8.3%) with oral NTX, 7596 (72%) with buprenorphine, and 1916 (18.2%) with methadone. Patients in the XR-NTX group were more likely to be male (75% vs 58.7%, 64.1%, and 51.4%, respectively; all P <.01) and tended to reside in the eastern part of the United States relative to the other groups (37.8% vs 30.2%, P = .06; 30.4%, P <.05; and 14.2%, P <.0001, respectively). They were older (36.9 years) compared with patients who received oral NTX (34.2; P = .02) or buprenorphine (34.8; P = .06), but younger relative to methadone users (42.3%; P <.0001). The XR-NTX group had significantly fewer patients with the lowest socioeconomic score relative to all 3 oral medication groups (18.6% vs 31.7%, 26.0%, and 32.9%, respectively; all P <.05).

Patient pre-index clinical characteristics in the 4 opioid medication groups are presented in **Table 3**. Although the distribution was similar among the other groups, patients given buprenorphine appeared to be healthier at the baseline, with significantly fewer patients with an Elixhauser index score of 3 or greater, and fewer distinct psychiatric diagnoses and medications.

Patients in the XR-NTX cohort spent significantly more days in a detoxification facility (2391 per 1000 patients) relative to those in the buprenorphine (1188) and methadone (301) cohorts. Similarly, the number of patients admitted to detoxification and/or rehabilitation centers at baseline was greater for those given XR-NTX (353) versus those given buprenorphine (212) and methadone (53). This translated into a higher cost for detoxification and rehabilitation at baseline in patients receiving XR-NTX. Outpatient resource use and cost were similar among the groups at baseline, excepting significantly greater opioid-related outpatient physician visits and costs and significantly less non–opioid-related outpatient visits and costs in the XR-NTX group compared with the methadone group.

Total healthcare cost during the 6-month pre-index period for patients in the XR-NTX group was significantly higher versus the buprenorphine group, but lower versus the methadone group. Among opioid-dependent patients at baseline, there were no significant differences in costs between the XR-NTX and oral NTX groups.

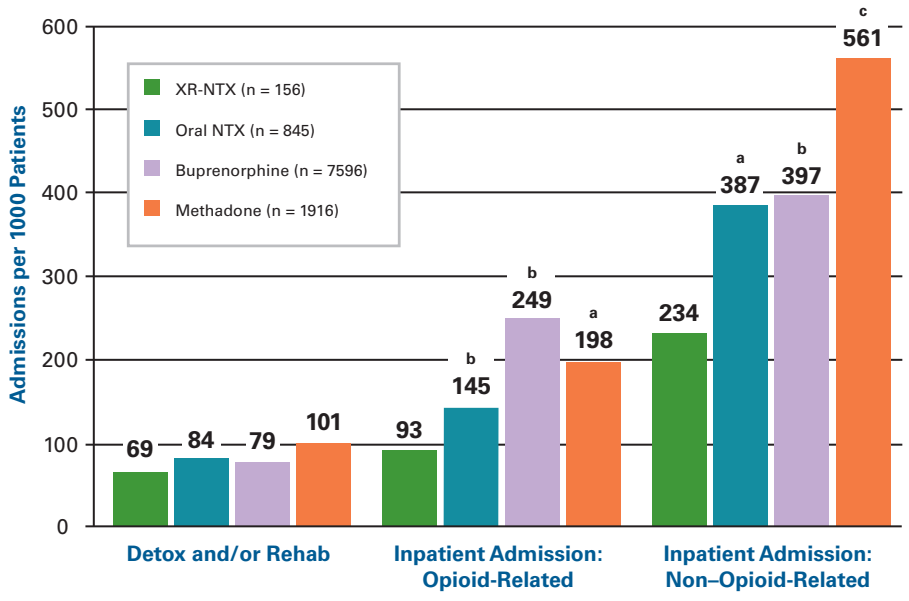
Overall, the XR-NTX group showed notable cohort differences, including a greater percentage of patients who were male, were from the eastern United States, had higher socioeconomic status, and had higher utilization rates for physician services and detoxification. This pattern indicated a substantial degree of prescribing bias, consistent with the fact that XR-NTX was not yet approved by the FDA for the prevention of relapse to opioid dependence following detoxification. Baseline differences among the opioid treatment groups were controlled using the instrumental variable approach; risk-adjusted outcomes are presented in **Figure 2** and **Table 4**.

Compared with patients given oral NTX, those given XR-NTX had a greater number of refill persistence days (55 vs 61 days, respectively), fewer distinct psychiatric medications (2.34 vs 1.99, respectively), fewer detoxification days (71 vs 62 per 1000 patients, respectively), fewer detoxification or rehabilitation admissions (84 vs 69, respectively), fewer ED visits (767 vs 608, respectively), and significantly fewer opioid-related inpatient admission rates (145 vs 93, respectively) and non–opioid-related inpatient admission rates (387 vs 234, respectively) (Figure 2A).

The overall healthcare costs for patients given XR-NTX were not different from those given buprenorphine,

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

A. Inpatient Admissions per 1000 Patients:
Instrumental Variable Matched Outcomes 6 Months After Index Date



B. Inpatient Costs per Patient:
Instrumental Variable Matched Outcomes 6 Months After Index Date

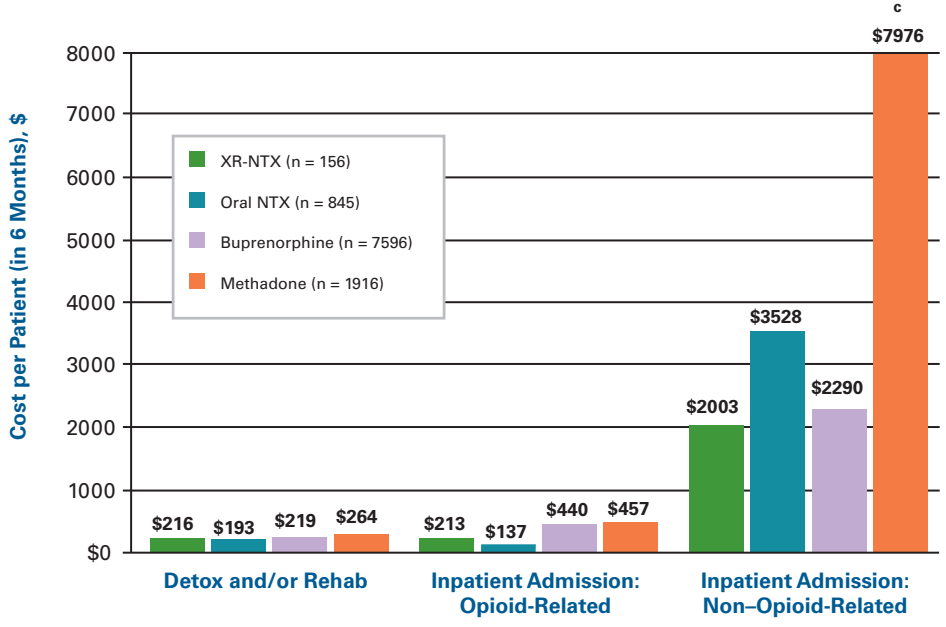
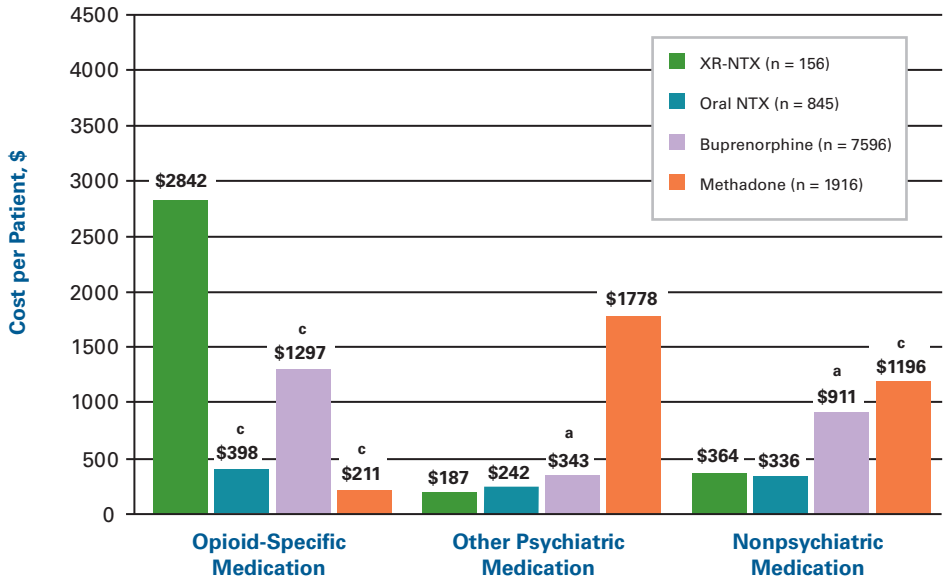
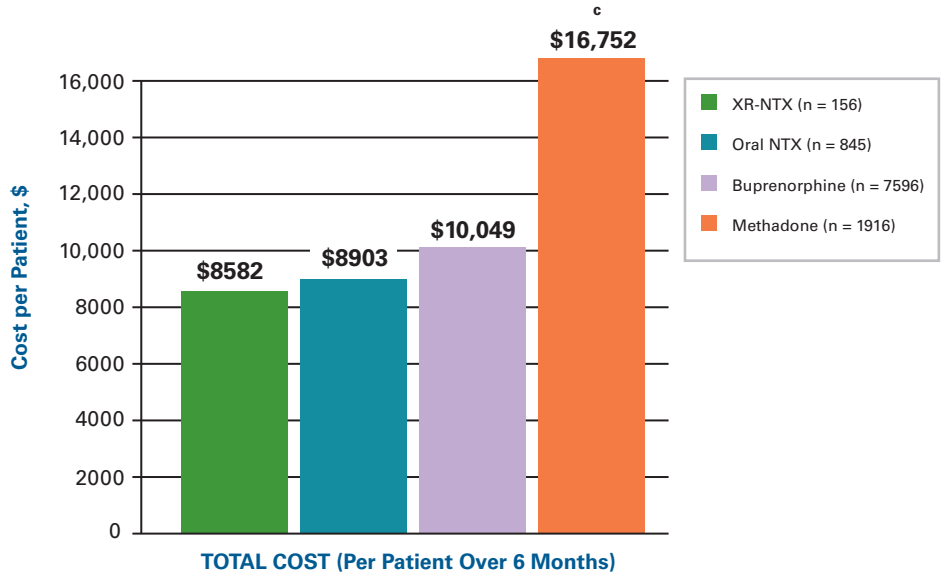


Figure 2. Opioid-Dependence Pharmacotherapies: Health Economic Outcomes 6 Months After Index Date *(Continued)*

C. Pharmacy Costs per Patient:
Instrumental Variable Matched Outcomes 6 Months After Index Date



D. Total Cost per Patient (inpatient + outpatient + pharmacy costs):
Instrumental Variable Matched Outcomes 6 Months After Index Date



NTX indicates naltrexone; XR-NTX, extended-release injectable naltrexone.
P vs XR-NTX:
[a] *P* <.05.
[b] *P* <.01.
[c] *P* <.001.

Table 4. Risk-Adjusted Outcomes Measures in Opioid-Dependent Patients by Pharmacotherapy

Post-Index Period	Opioid Dependence Medication						
	XR-NTX (n = 156)	Oral NTX (n = 845)		Buprenorphine (n = 7596)		Methadone (n = 1916)	
Compliance and persistence with therapy	%	%	*P*	%	*P*	%	*P*
Continuous MPR ≥0.8	21	8	**<.0001**	34	**.0105**	29	.0959
Outcome	Mean	Mean	*P*	Mean	*P*	Mean	*P*
Persistence days with index medication	61.49	54.98	.229	68.92	0.142	62.8	.798
Post-index number of distinct psychiatric diagnoses	3.52	3.47	.727	3.12	**.004**	2.7	**<.0001**
Post-index number of distinct psychiatric medications	1.99	2.34	.062	2.59	**.001**	2.72	**<.0001**
Healthcare utilization							
Post-index number of detoxification facility visits (number of visits/1000 patients)	62	71	.672	66	.851	82	.333
Post-index inpatient (number of admissions/1000 patients)							
Detoxification and/or rehabilitation	69	84	.61	79	.704	101	.243
Opioid-related inpatient admission	93	145	**.005**	249	**.007**	198	**.025**
Non–opioid-related inpatient admission	234	387	**.027**	397	**.001**	561	**<.0001**
Post-index outpatient (number of visits/1000 patients)							
Emergency department visits	608	767	.575	1092	.067	1590	**<.0001**
Opioid-related and physician provider	869	395	.173	1362	.13	452	.208
Opioid-related and substance abuse psychosocial provider	528	452	.705	391	.465	241	.132
Non–opioid-related outpatient	16,654	16,338	.824	16,840	.889	22,054	**<.0001**
Costs (per patient)							
Post-index inpatient							
Cost of detoxification and/or rehabilitation	$216	$193	.571	$219	.721	$264	.619
Cost of opioid-related inpatient admission	$213	$137	.725	$440	.263	$457	.235
Cost of non–opioid-related inpatient admission	$2003	$3528	.296	$2290	.834	$7976	**<.0001**
Post-index outpatient							
Cost of emergency department visits	$184	$283	.409	$402	.051	$462	**.014**
Cost of opioid-related and physician provider	$95	$6	.077	$150	.243	$52	.37
Cost of opioid-related and substance abuse psychosocial provider	$29	$267	.903	$34	.782	$22	.735
Cost of non–opioid-related	$4510	$4068	.248	$3678	**.025**	$6173	**.0005**
Post-index pharmacy							
Cost of FDA-approved opioid-dependence medications	$2842	$398	**<.0001**	$1297	**<.0001**	$211	**<.0001**
Cost of other psychiatric medications	$187	$242	.431	$343	**.017**	$1778	.888
Cost of nonpsychiatric medications	$364	$336	.904	$911	**.014**	$1196	**<.0001**
Total cost (per patient = inpatient, outpatient, and pharmacy)	$8582	$8903	.867	$10,049	.414	$16,752	**<.0001**

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

despite significantly greater costs for the FDA-approved opioid-dependence medication ($2842 vs $1297, respectively)(Figure 2C). Patients receiving buprenorphine had greater refill persistence than those receiving XR-NTX (69 vs 61 days, respectively), but had significantly more opioid-related inpatient admissions (249 vs 93 per 1000 patients, respectively) (Figure 2A), more non–opioid-related inpatient admissions (397 vs 234, respectively) (Figure 2A), and more ED visits (1092 vs 608, respectively).

Given these overall utilization differences and their related costs, the overall healthcare costs per patient in the group treated with methadone were significantly greater than those with XR-NTX ($16,752 vs $8582, respectively) (Figure 2D), despite the significantly lower cost for the opioid dependence pharmacotherapy ($211 vs $2842, respectively) (Figure 2C). Patients given methadone or XR-NTX showed similar prescription persistence. Compared with patients given XR-NTX, those given methadone had a significantly greater number of distinct psychiatric diagnoses, but lower use of distinct psychiatric medications. Also, patients receiving methadone spent more days in detoxification (82 vs 62 per 1000 patients, respectively), had more detoxification or rehabilitation admissions (101 vs 69, respectively) (Figure 2A), had more opioid-related inpatient admissions (198 vs 93, respectively) (Figure 2A), had significantly more ED visits (1590 vs 608, respectively), and had significantly more non–opioid-related outpatient visits (22,054 vs 16,654, respectively) compared with those receiving XR-NTX.

Discussion

The combined data from these 2 large insurance data sets made possible the first study to date examining healthcare costs and utilization for the full set of currently available opioid-dependence treatments. This risk-adjusted analysis compared outcomes in 13,316 patients who received any versus no medication for opioid-dependence disorder and 10,513 patients who received 1 of the 4 FDA-approved pharmacologic therapies. Thus, this study was one of the largest health economic studies in this disorder to date, and the first such study to analyze treatment with XR-NTX. The study was a comprehensive analysis of total healthcare costs paid and corresponding healthcare service utilization. Compared with opioid-dependence treatment that did not include medication, medication-assisted treatment was associated with significantly fewer admissions for detoxification and/or rehabilitation, opioid-related inpatient medical care, and non–opioid-related inpatient medical care. In all of these inpatient service categories, costs were significantly lower in patients who received a medication, and total healthcare costs, including inpatient, outpatient, and pharmacy costs, were 29% lower for patients who received a medication for their opioid dependence, despite significantly higher costs for medications. Patients given XR-NTX had significantly fewer opioid-related and non–opioid-related hospitalizations than those given any of the 3 oral agents, fewer ED visits than patients who received methadone, and an overall pattern of the lowest use in all categories of inpatient utilization (Figure 2A). Despite significantly higher costs for XR-NTX, total healthcare costs, including inpatient, outpatient, and pharmacy costs, were not significantly greater than total costs with oral NTX or buprenorphine, and were 49% lower than with methadone (Figure 2D).

This retrospective claims analysis lacked clinical variables such as drug use, severity, and overdose; however, the rate of hospital admissions is an intensive utilization variable that may also represent a proxy for morbidity, which has importance in addition to cost implications. In this study, medication was associated with 29% lower costs than nonpharmacologic treatment, whereas the relative risk reduction associated with medication was 84% for opioid-related hospitalization and 60% for non–opioid-related admission. Of the 4 FDA-approved medications, the total cost associated with XR-NTX was not significantly different from oral NTX and buprenorphine, and it was 49% lower than that with methadone. However, Figure 2A shows that the risk of an opioid-related hospitalization in patients given XR-NTX was 36% lower than that with oral NTX, 63% less than with buprenorphine, and 53% less than with methadone; the risk for non–opioid-related hospitalization with XR-NTX was 40%, 41%, and 58% lower than that with oral NTX, buprenorphine, and methadone, respectively. Similar results have been reported in the treatment of alcohol dependence, with 3 large retrospective claims analyses showing that medication-assisted treatment was associated with lower total healthcare costs than nonmedication treatment.[29-31] Also, XR-NTX treatment cohorts demonstrated utilization and/or cost benefits in relation to approved oral agents for alcohol dependence.

These overall healthcare cost results highlight the problem of healthcare budget segmentation. The any medication group had total medication costs that were several times greater than those with no anti-opioid medications; however, overall healthcare costs were 29% less in those receiving opioid-dependence medication. Likewise, the cost of XR-NTX itself was more than 10-fold that of methadone, but total healthcare costs associated with methadone were nearly double those of XR-NTX. While many other factors must be taken into account, these findings suggest that stand-alone budgeting based on pharmacy costs may be counterproduc-

tive in addiction treatment—the cost offsets of a "carve out" arrangement may not accrue to medical cost centers.

Refill persistence and outcomes showed an inverse relationship among once-monthly XR-NTX and daily oral NTX. Once XR-NTX is administered by a healthcare professional, the active ingredient, NTX, is present for a month and cannot be removed from the system. Daily oral NTX, however, was found to be ineffective due to poor treatment adherence.[32] In the present study, 21% of patients receiving XR-NTX possessed the injection at least 80% of the study days, a percentage which was 2.6 times that with oral NTX (8%). The XR-NTX group had significantly fewer opioid-related and non–opioid-related hospitalizations. Compared with patients given XR-NTX, those given methadone or buprenorphine had similar refill persistence, and a greater percentage of these patients possessed their medication for at least 80% of the duration. This may reflect patient satisfaction, treatment effectiveness, and/or the fact that both agents have agonist properties that maintain opioid physical dependence and result in symptoms of withdrawal upon cessation.

Limitations of retrospective claims analyses include the absence of randomized controls. Therefore, treatment assignment resulted in imbalances in important clinical variables. There were substantial differences between the cohorts at baseline, some of which may have been unobserved (eg, differential patient motivation or provider characteristics). Possible reasons for these differences include regional differences in access to methadone and buprenorphine, differential reimbursement, and provider and community attitudes toward opioid-maintenance therapy and patient self-selection (eg, orientation toward an opioid-free recovery). These differences were particularly salient because at the time of data collection, XR-NTX was not yet approved by the FDA for opioid-dependence treatment, resulting in a notably smaller cohort receiving this medication. Patients who were seeking XR-NTX and prescribers offering it were possibly quite different from patients and providers utilizing other agents. The statistical methods we used, while designed to adjust for observed and unobserved differences and bias, may have been imperfect in this respect, and thus the observed findings may reflect unadjusted confounding.

Another limitation was that group sizes varied considerably in this study and, in general, studies of the relationship between rare exposures to a risk factor require large sample sizes to obtain reasonable estimates. The sample size for the XR-NTX group in particular was smaller than the other groups, raising questions about generalizability and the interpretation of statistical tests. However, the overall sample size was large, and the findings of the highest cost incidents for the XR-NTX comparisons show relatively good internal consistency, supporting the validity of the findings for this XR-NTX sample. Further research, however, should be conducted with larger samples for confirmation, now that XR-NTX is FDA-approved for opioid dependence. The index date for the any medication group permitted inclusion of a period of psychosocial treatment prior to medication-assisted treatment (in contrast to the no medication group), possibly leading to underestimated costs for the treatment episode in the medication group. We excluded patients who transitioned from one medication to another. It is not known what percentage of patients given oral NTX were subject to mandated or monitored administration (ie, to retain a professional license), what percentage of patients given buprenorphine intended to undergo detoxification only, or what percentage of patients given methadone were treated in a licensed methadone maintenance clinic versus receiving methadone for the treatment of pain outside of an opioid treatment program. Claims data do not record duration of opioid dependence or assessments of ongoing illicit drug use. No information was available regarding recommended or adequate durations of treatment, and daily treatment adherence could not be inferred by prescription refills. Medications have adverse effects, some of which are noted in boxed warnings in the prescribing information, and adverse effects differ between the oral and injectable agents; adverse events data were not examined. The 6-month study period did not provide long-term outcome data, and the patient population had some distinct characteristics, including having commercial insurance for a full year.

The study had some relevant strengths, despite these limitations. To establish comparability between cohorts, propensity-score matching was used for the any versus no medication comparison, and instrumental variable analysis was added to the 4-way medication comparison to control for both observed and unobserved bias. Refill possession duration was relatively brief, but this duration was real, and treatment effects were therefore examined during and beyond the average medication treatment duration. A good degree of internal consistency was apparent in the patterns of higher utilization of intensive services for the comparisons of no medication versus any medication and the 3 oral agents versus XR-NTX. Patients in this study were commercially insured and XR-NTX had yet to receive FDA approval for the treatment of opioid dependence; nevertheless, from the perspective of commercial insurance, these results would be expected to have external validity, given the large sample sizes for the no medication and oral medication cohorts, which consisted of real-world patients treated by community providers in standard treatment settings. Opioid agonist treatment in the

United States has traditionally been government funded, but 33.1% to 61.6% of public programs now report commercial insurance funding[33] and increasing commercial coverage is part of the National Drug Control Strategy.[3]

The vast majority (98.5%) of 270,881 patients enrolled in US opioid treatment programs are receiving methadone.[33] In the United States, the annual cost for counseling plus methadone services is at least $4700, whereas the combined mean costs of methadone plus opioid-related physician and psychosocial services in this study over 6 months was much less, suggesting that these data may underestimate the difference between XR-NTX and methadone costs.[1,34] Furthermore, this study raises a question about the medical care of patients receiving methadone. These data show a low use of physician providers and a very high use of ED services in patients given methadone, raising a quality-of-care issue that is worthy of further exploration.

This study's cost evaluation was limited to direct healthcare expenditures, but a review of 11 studies found that the largest source of cost benefit associated with substance abuse treatment was reduction in criminal activity, followed by improved earning potential; the contribution from healthcare was third.[35] Future studies should include these cost areas.

Regulatory, licensing, and financing policies have separated treatment of opioid addiction from medical care, significantly limiting access to care and further stigmatizing both individuals with these addictions and pharmacotherapy itself. For many years, it has been easier for individuals to acquire drugs than to receive treatment for addiction. The integration of opioid-dependence treatment into mainstream medicine is a key component of the White House's national drug strategy, but the barriers are numerous—training deficits, organizational obstacles, negative attitudes toward addictions, and fears about additional costs.[3] While methadone is limited to specially licensed programs, the other agents can be delivered in any clinical setting (eg, office-based physician practices and community health centers). Based on pretreatment comorbidity and utilization, patients in this study who received medication tended to be sicker at baseline. This supports the need for physician involvement in the care of patients with addiction. With medical treatment, total costs and use of inpatient services of all types were lower, supporting the potential cost benefit of increased integration of addiction and primary care services. This has been previously demonstrated in patients with substance abuse–related medical conditions.[36]

The majority of patients with opioid-dependence disorder in the United States remain untreated. Yet, the literature on cost-benefit studies with opioid agonist maintenance therapy consistently finds that benefits exceed costs, even when not all benefits are accounted for in the analysis.[37,38] The National Institute on Drug Abuse guide states that no single treatment is appropriate for all patients, that treatment needs to be readily available, and that medications are an important treatment element, in combination with behavioral approaches.[1] Further research is needed, with larger XR-NTX populations, for longer durations, and preferably with prospective designs or cohort-matching methods analogous to what were utilized in the present study. The current findings regarding opioid-dependence pharmacotherapy are compelling, and the cost findings regarding XR-NTX deserve further exploration in larger cohorts and trials using experimental designs that collect treatment outcome and cost data.

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

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