

Cost of Pharmacotherapy for Opioid Use Disorders Following Inpatient Detoxification

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Addressing opioid use disorders (OUDs), heroin and fentanyl use, and escalating rates of overdose deaths in the United States is a top priority among clinicians, policy makers, payers, and other stakeholders.¹ The latest statistics on opioid overdose rates are staggering, showing a national increase of 30% from 2016 to 2017.² Opioid agonist and antagonist medications are the recommended first line of treatment for OUDs.^{3,4} FDA-approved medications for OUDs currently include methadone, buprenorphine, and naltrexone.⁵ Both naltrexone and buprenorphine have short- and long-acting formulations. Whereas methadone can be dispensed only from approved facilities, buprenorphine and naltrexone can be prescribed by a physician or other practitioner with prescribing privileges, such as a nurse practitioner or physician assistant (PA).

Recent clinical trials have established similar effectiveness of these medications in preventing relapse up to 6 months among those who successfully initiate treatment post detoxification.^{6,7} Adoption of these medications by treatment providers is low, however, and reimbursement for these medications varies considerably among private and public payers.⁸ Other provider concerns, such as staff burden, increased practice costs, large patient caseloads, and long-term effectiveness, may also contribute to limited adoption.⁹

As new evidence regarding the effectiveness and cost-effectiveness of these treatments is established, providers, payers, and other stakeholders need to understand the resources and associated costs of implementation and ongoing provision of different treatment models. This information can help address and quantify some of the barriers to adoption by enumerating the types of resources required to successfully provide treatment, categories of expenditures (eg, training, staff time, special equipment), and total expected annual and per-patient costs.

This study describes the approach and results of a comprehensive multisite cost analysis of the first head-to-head randomized clinical trial in the United States of extended-release injectable naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX) for preventing opioid relapse (NCT02032433).⁷ Our objective was to provide rigorous estimates of the costs of introducing pharmacotherapy treatment at the programs, inpatient detoxification, and

ABSTRACT

OBJECTIVES: To estimate the costs of providing extended-release injectable naltrexone (XR-NTX) and buprenorphine-naloxone (BUP-NX) following inpatient detoxification using data derived from a multisite randomized controlled trial at 8 US community-based treatment programs.

STUDY DESIGN: Cost data were collected for 3 intervention phases: program start-up, inpatient detoxification, and up to 24 weeks of medication induction and management visits (post detoxification). Cost analyses were from the healthcare sector perspective (2015 US\$); patient costs are also reported.

METHODS: We conducted site visits, administered a cost survey to treatment programs, and analyzed study data on medication and services utilization. Nationally representative sources were used to estimate unit costs. Uncertainty was evaluated in sensitivity analyses.

RESULTS: Mean start-up costs were \$1071 per program for XR-NTX and \$828 per program for BUP-NX. Mean costs per participant were \$5416 for XR-NTX (57% detoxification, 37% medication, 3% provider, 3% patient) and \$4148 for BUP-NX (64% detoxification, 12% medication, 10% provider, 14% patient). Total cost per participant ranged by site from \$2979 to \$8963 for XR-NTX and from \$2521 to \$6486 for BUP-NX.

CONCLUSIONS: For treatment providers, offering XR-NTX and/or BUP-NX as part of existing detoxification treatment modalities generates modest costs in addition to the costs of detoxification, which vary substantially among the 8 sites. From the patient's perspective, the costs associated with medication management visits may be a barrier for some individuals considering these treatments.

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medication management (MM) visits over the 24-week intervention phase, highlighting the variation in these costs across sites.

STUDY DESIGN

The cost analysis was conducted alongside the NIDA Clinical Trials Network CTN-0051: Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT) trial, a multisite, 2-arm, open-label, randomized controlled trial that tested the effectiveness of XR-NTX versus BUP-NX with regard to patient survival, free of opioid relapse, at 24 weeks.¹⁰ Participants (n = 570) were recruited from 8 US community-based inpatient detoxification or short-term residential treatment programs and randomized 1:1 to XR-NTX (n = 283) or BUP-NX (n = 287). Participant-level data (eg, intervention medication dispensing/administration, opioid relapse) were collected at each study visit as part of the main X:BOT protocol, whereas economic data on the costs of providing inpatient detoxification, XR-NTX and BUP-NX medications, and MM, as well as the time and travel costs incurred by study participants, were collected from agency research and clinical staff at in-person site visits.

METHODS

Analytic Overview

We employed a microcosting approach from the healthcare sector and patient perspectives.^{11,12} The costs of research-related activities were excluded.¹³ Resource utilization and expenditures were categorized by 3 distinct X:BOT study phases: setup/preimplementation (eg, training and other preparations needed to offer the medications), inpatient/residential detoxification treatment, and the intervention phase following randomization to XR-NTX or BUP-NX (medication induction and up to 24 weeks of MM).

Across all sites, cost estimates per participant are reported as means for future economic evaluation purposes and as medians/interquartile ranges for programmatic comparison.¹² Cost data were collected for fiscal years 2015 or 2016 and were adjusted using the consumer price index for all consumer goods and reported in 2015 US dollars.^{12,13} The Weill Cornell Medical College Institutional Review Board reviewed and approved study procedures. Cost data were analyzed in Microsoft Excel 2013 (Microsoft Corp; Redmond, Washington) and Stata 15.1 (Stata Corp; College Station, Texas).

Site-Level Data Collection and Analysis

A modified Drug Abuse Treatment Cost Analysis Program (DATCAP) instrument, available through the public domain, was used to identify and measure the program resources required to deliver XR-NTX and BUP-NX at each site. The DATCAP is a flexible program-level costing instrument that has been used in numerous economic studies of substance use disorder (SUD) treatment and related programs.¹⁴ For each intervention phase, the survey captured the costs associated

TAKEAWAY POINTS

- ▶ Offering extended-release injectable naltrexone and/or buprenorphine-naloxone as part of existing detoxification treatment generated modest costs beyond the cost of inpatient detoxification.
- ▶ From the patient's perspective, the costs associated with medication management visits may be a barrier for some individuals considering these treatments.

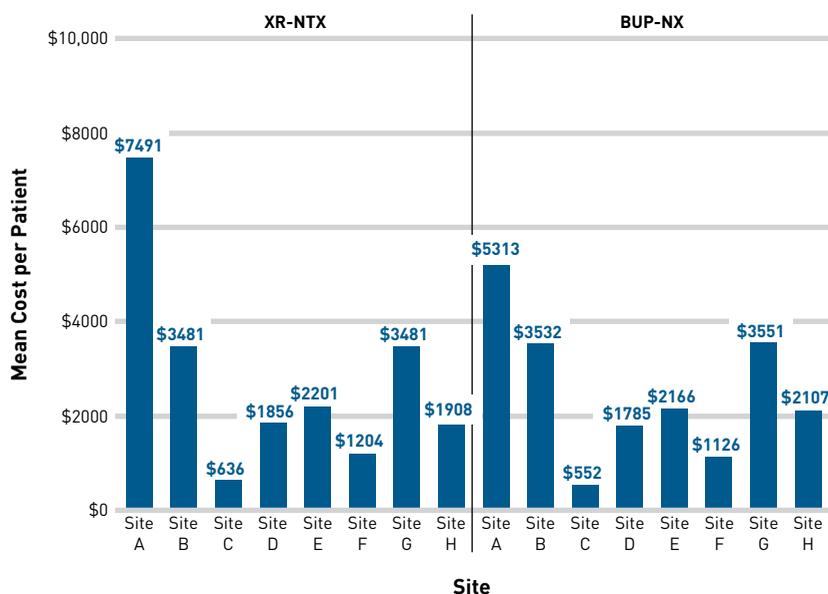
with the following resource categories, as applicable: personnel (clinicians, staff), buildings/space, contracted services, equipment, supplies, and miscellaneous inputs, including donated resources. The cost survey was sent to all study sites, and a preliminary conference call was scheduled to discuss the procedures for collecting cost data. An in-person site visit was also conducted to review the information provided in the survey, address gaps and questions, and finalize cost data collection. Site visits were conducted at all sites and generally lasted 1 day, during which the investigative team met with research, administrative, and clinical staff. Data on staff time and activities pertaining to XR-NTX and BUP-NX medication administration and management during the trial were collected through interviews with site clinical and research staff. Other relevant cost data were assembled directly from agency expenditure reports and financial records.

Start-up costs were one-time investments that included staff training (time spent attending in-person or web-based training) and the cost of any equipment or supplies that needed to be purchased. For example, 2 agencies did not offer XR-NTX before participating in the trial and therefore incurred additional costs for purchasing a refrigerator to store medications.

Cost data for detoxification services were collected for the 2015 fiscal year (July 2014-June 2015 or September 2014-August 2015). This time frame is consistent with the intervention steady state period, when intervention activities and participant case flow were stable. One site provided 2015-2016 expenditure data but noted that these expenditures did not vary significantly from previous years. Two sites offered step-down detoxification services (1 ambulatory detoxification, 1 residential social rehabilitation program). The cost analysis results presented here did not include the costs of these step-down programs because we were unable to confirm the percentage of trial participants transitioning to these programs and did not have information on mean length of stay or mean daily census.

Estimates include the annual cost of detoxification, mean daily census, mean daily cost per detoxification patient, mean length of stay, and mean detoxification costs per episode. The total annual costs for detoxification were divided by the mean daily census in the program for all patients to calculate the mean annual cost per patient, which can also be reported as the mean daily cost per patient. The mean daily cost was multiplied by the mean length of stay in days for XR-NTX and BUP-NX participants to calculate the mean cost per detoxification episode for each study arm.

Costs during the intervention phase were calculated from study records on services and medications utilized for the induction visit

FIGURE. Inpatient Detoxification Costs per Patient (2015 US\$)

BUP-NX indicates buprenorphine-naloxone; XR-NTX, extended-release injectable naltrexone.

(immediately following detoxification) and follow-up MM visits. These costs were primarily for provider and patient time, medication costs, and patient travel costs. For patient travel costs, sites provided an estimate of the proportion of participants traveling by public transportation versus driving. For patients taking public transportation, the local base metro/bus fare was used to estimate the cost of traveling to an MM visit in each city. For participants who were driving, some sites estimated the mileage patients traveled from their residences, whereas other sites estimated mileage from central landmarks in the neighborhoods where participants lived (eg, post office or city center). We then used Google Maps¹⁵ to estimate the mean travel distance and time to the treatment facility.

Cost Calculations

For purposes of generalizability, we estimated the labor cost of delivering the intervention by assigning the relevant wage and fringe benefit rates from the Bureau of Labor Statistics to the time estimates for each provider and staff member (eAppendix Table 1 [eAppendix available at ajmc.com]).¹⁶ We used the federal minimum wage to value patient time, given that the majority of patients were unemployed or employed in part-time, low-wage jobs.⁷ Internal Revenue Service standard mileage reimbursement rates from the American Automobile Association were used to value the direct costs of patient travel.¹⁷ As recommended by the Second Panel on Cost-Effectiveness in Health and Medicine,¹² medication costs came from the Federal Supply Schedule. The cost of an XR-NTX injection was \$704, and the mean cost of generic BUP-NX was \$1.20 for 4 mg and \$2.17 for 8 mg.¹⁸

Sensitivity Analysis

Sensitivity analyses included substituting higher medication costs that may be faced by some private insurance payers or Medicare, represented by the wholesale acquisition cost (WAC) of XR-NTX (\$1309/injection) and branded BUP-NX film (\$5.09/4-mg film), and limiting the sample to participants who successfully initiated their randomized treatment (ie, per-protocol sample for XR-NTX [n = 204] and BUP-NX [n = 270]).

RESULTS

The mean cost of inpatient detoxification was \$412 per patient day and varied considerably across sites, as reported in eAppendix Table 2 (range, \$115-\$1172). Patients in the XR-NTX arm stayed a mean (SD) of 8.0 (5.3) days, whereas patients in the BUP-NX arm stayed 7.5 (5.1) days. Within sites, the mean length of stay was similar between BUP-NX and XR-NTX; site B had the longest mean length of stay (approximately 14 days), and site H had the shortest (approximately

3 days). The mean (SD) detoxification episode cost per XR-NTX participant at each site ranged from \$636 (\$484) to \$7491 (\$2112) and per BUP-NX participant at each site ranged from \$552 (\$126) to \$5313 (\$1576) (Figure; eAppendix Table 2). Site A had the highest mean cost per detoxification episode for both BUP-NX and XR-NTX, driven primarily by the relatively higher cost per detoxification day, although length of stay was lower than at many of the other sites.

Table 1 presents a breakdown of provider and patient time spent on the XR-NTX or BUP-NX induction visit and follow-up MM visits, including the mean time it took patients to travel to and from the MM visits. Induction visits involved more medical oversight and took longer than MM visits. MM visits were expected to occur weekly for the first month, then biweekly for 3 months, and monthly for the last 2 months of the trial. In most cases, participants met with 2 providers during each visit—1 clinician (physician, PA, or registered nurse) and 1 counselor. The mean (SD) time for XR-NTX induction was 144 (80) minutes (range, 30-248). This was slightly longer, at most sites, than the time required for induction onto BUP-NX (mean [SD] = 134 [106] minutes; range, 10-180). One exception was for site E, which reported 360 minutes for induction onto BUP-NX, split about evenly between time spent with the physician and counselor. The mean (SD) time per MM visit was 66 (38) minutes (range, 23-135) for XR-NTX and 64 (40) minutes (range, 23-135) for BUP-NX. Patient travel time (1 way) ranged from 13 minutes to 62 minutes (mean [SD] = 38 [18] minutes).

Table 2 presents each component of total intervention costs for XR-NTX and BUP-NX for all sites. Start-up costs are reported at the site level; all other intervention costs are reported as the mean cost per

TABLE 1. Medication Induction and Management: Provider Type, Time per Visit, and Patient Travel Time

Site Characteristic	Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Mean (SD) for All Sites	Median (IQR) for All Sites
Provider										
Type ^a	MD, counselor	MD, RN	PA, NP, counselor	PA, counselor	NP, RN, counselor	RN, counselor	MD, RN, counselor	MD or DO, PA, counselor	N/A	N/A
Mean total time per visit (minutes)										
XR-NTX										
Induction	30	248	120	90	210	180	60	210	144 (80)	150 (128)
MM	23	43	70	45	75	135	32.5	105	66 (38)	58 (42)
BUP-NX										
Induction	10	150	75	120	360	120	60	180	134 (106)	120 (86)
MM	23	28	70	45	75	135	33	105	64 (40)	58 (51)
Mean patient travel time, 1 way (minutes) ^b										
XR-NTX or BUP-NX	53	26	62	13	22	33	36	57	38 (18)	35 (29)

BUP-NX indicates buprenorphine-naloxone; DO, doctor of osteopathic medicine; IQR, interquartile range; MD, doctor of medicine; MM, medication management follow-up visit; N/A, not applicable; NP, nurse practitioner; PA, physician assistant; RN, registered nurse; XR-NTX, extended-release injectable naltrexone.

^aIn most cases, participants met with 2 providers during each visit—1 clinician (physician, PA, or RN) and 1 counselor.

^bMean patient travel time is for follow-up MM visits specifically, which did not vary by study arm.

participant (detoxification, provider visit, medication, and patient). The mean (SD) program start-up costs were \$1071 (\$682) for XR-NTX (range, \$251-\$2387) and \$780 (\$515) for BUP-NX (range, \$91-\$1710). The higher start-up costs associated with XR-NTX result from the greater training time required for providing an injectable medication versus oral medication, as reported in our site surveys and interviews.

For XR-NTX, mean total intervention costs per participant at each site ranged from \$2979 to \$8963, with a mean (SD) of \$5416 (\$2969) across all sites. The mean total intervention costs per participant for BUP-NX at each site ranged from \$2522 to \$6485, with a mean (SD) of \$4148 (\$1987) across all sites. Mean total costs for XR-NTX consisted primarily of the cost of detoxification (\$3070, or 57% of total costs) and medication (\$2003, or 37%); provider and patient costs were a small proportion of the total intervention cost (both about 3% of total costs). For BUP-NX, detoxification was also the main driver of total intervention cost (\$2663, or 64% of total costs); medication costs were lower (\$479, or 12%), whereas provider and patient costs were higher (together ranging from 10%-14% of total costs) due to more frequent visits.

When valuing medication at the WAC, the cost of XR-NTX increased to a mean of \$4341 per patient, representing an 117% increase in medication cost and an increase of 43% in total intervention cost. Similarly, applying the BUP-NX film pricing increased the mean per-patient cost of the BUP-NX arm to \$2362, representing a 393% increase in medication cost and a 45% increase in total intervention cost (see Table 2 notes). Total costs based on data collected from the per-protocol sample (ie, those successfully inducted to XR-NTX or BUP-NX) were consistently higher than those based on the intention-to-treat sample for XR-NTX but remained the same or similar for BUP-NX (intention-to-treat results in Table 2; per-protocol results in [eAppendix Table 3](#)).

DISCUSSION

This paper presented the results of the first multisite cost analysis of XR-NTX versus BUP-NX treatment for patients initiating inpatient or residential detoxification for OUD, an important contribution given the limited information on the cost of implementing pharmacotherapy for patients with OUDs and concerns about financial or other barriers to adoption by providers and patients.^{19,20} The cost analysis was conducted prospectively alongside the first US randomized controlled comparative effectiveness trial of these medications in the treatment of OUDs.⁷ The study provided a careful accounting of the costs required to implement XR-NTX and BUP-NX into standard detoxification treatment and over a 24-week intervention period, overall and by site, including costs incurred by patients.

Substantial variability in total intervention costs was noted across sites, driven largely by the variation in inpatient detoxification costs. In 5 of the 8 sites, more than 50% of total intervention costs were attributable to inpatient detoxification services. Such variation is not surprising considering the geographic and organizational differences across the participating treatment providers. For instance, treatment capacity, patient need, referral process, and financing for SUD treatment were different across sites and affected mean daily census in the detoxification programs. These factors are in turn determined by agency size and location, sources of funding (eg, Medicaid, private donations, grants), and state policies on prescribing practices and Medicaid reimbursement for OUD medications.

There was also variation among sites in provider time to conduct induction and MM but minimal variation in patient visit time within sites. Except for site A, induction to XR-NTX required more than an hour—in many cases, more than 3 hours. MM visits were generally shorter in duration, but mean visit length ranged from 23 minutes at site A to more than 2 hours at site F. Sites reported that MM visits

METHODS

TABLE 2. Start-Up and Intervention Costs for XR-NTX and BUP-NX, ITT Outcomes (2015 US\$)^a

Cost Component	Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Mean (SD) for All Sites	Median (IQR) for All Sites
Start-up costs, site-level										
XR-NTX	\$980	\$853	\$509	\$2387	\$593	\$904	\$1580	\$251	\$1071 (\$682)	\$879 (\$558)
BUP-NX	\$800	\$750	\$448	\$1710	\$434	\$699	\$1305	\$91	\$780 (\$515)	\$725 (\$482)
Intervention costs, participant-level										
XR-NTX										
Detoxification, mean (SD)	\$7491 (\$2132)	\$3481 (\$1411)	\$636 (\$491)	\$1856 (\$1500)	\$2201 (\$592)	\$1204 (\$473)	\$3481 (\$1830)	\$1908 (\$899)	\$3070 (\$2559)	\$2151 (\$2712)
Provider, mean (SD)	\$60.26 (\$73.34)	\$210 (\$192)	\$165 (\$116)	\$138 (\$62.95)	\$203 (\$115)	\$238 (\$173)	\$54.36 (\$61.54)	\$307 (\$229)	\$160 (\$150)	\$126 (\$281)
Medication, mean (SD) ^b	\$1286 (\$1701)	\$1760 (\$1816)	\$1870 (\$1664)	\$2499 (\$1578)	\$2640 (\$1766)	\$2487 (\$1945)	\$1600 (\$1865)	\$2112 (\$1724)	\$2003 (\$1801)	\$1408 (\$4224)
Patient, mean	\$126	\$131	\$308	\$89	\$178	\$268	\$195	\$326	\$184 (\$77)	\$181 (\$143)
Total intervention cost, XR-NTX, mean (SD)	\$8963 (\$2988)	\$5582 (\$2784)	\$2979 (\$1824)	\$4582 (\$2244)	\$5222 (\$2052)	\$4197 (\$2240)	\$5331 (\$2608)	\$4653 (\$1918)	\$5416 (\$2969)	\$5375 (\$4111)
BUP-NX										
Detoxification, mean (SD)	\$5313 (\$1592)	\$3532 (\$1406)	\$552 (\$127)	\$1785 (\$1681)	\$2166 (\$382)	\$1126 (\$290)	\$3551 (\$1363)	\$2107 (\$1082)	\$2663 (\$1913)	\$2088 (\$2277)
Provider, mean (SD)	\$225 (\$128)	\$407 (\$130)	\$436 (\$230)	\$352 (\$124)	\$610 (\$211)	\$519 (\$593)	\$203 (\$117)	\$1136 (\$608)	\$434 (\$356)	\$364 (\$365)
Medication, mean (SD) ^c	\$574 (\$377)	\$432 (\$259)	\$573 (\$431)	\$527 (\$325)	\$535 (\$272)	\$252 (\$276)	\$414 (\$345)	\$488 (\$410)	\$479 (\$345)	\$465 (\$590)
Patient, mean	\$374	\$356	\$960	\$314	\$679	\$744	\$592	\$1004	\$581 (\$363)	\$466 (\$436)
Total intervention cost, BUP-NX, mean (SD)	\$6486 (\$1784)	\$4727 (\$1557)	\$2521 (\$1060)	\$2978 (\$1882)	\$3990 (\$875)	\$2641 (\$1343)	\$4760 (\$1562)	\$4735 (\$1663)	\$4148 (\$1987)	\$3851 (\$2414)

BUP-NX indicates buprenorphine-naloxone; IQR, interquartile range; ITT, intention-to-treat; WAC, wholesale acquisition cost; XR-NTX, extended-release injectable naltrexone.

^aMean total intervention costs are based on detoxification costs and costs incurred during the intervention phase for medication induction and management. The cost of XR-NTX and BUP-NX medications is included here.

^bIn sensitivity analyses, WAC estimates for XR-NTX were substituted, resulting in mean and median costs increasing from \$2003 to \$4341 and \$1408 to \$5236, respectively.

^cIn sensitivity analyses, WAC estimates for branded film formulation of BUP-NX were substituted, resulting in mean and median costs increasing from \$479 to \$2362 and \$465 to \$2275, respectively.

in which XR-NTX patients received an administration of injectable naltrexone took longer than other MM visits. This additional time cost along with the higher medication cost for XR-NTX were the main factors contributing to the higher mean total costs during the intervention phase for XR-NTX compared with BUP-NX. Total intervention costs are sensitive to different cost assumptions for XR-NTX and BUP-NX. Medicare Part D plans, for example, would likely pay the WAC for these medications, which would increase total intervention costs for both XR-NTX and BUP-NX.

Complete detoxification from opioids was mandatory for patients initiating XR-NTX, which required additional steps such as a naloxone challenge to confirm that a patient was free of opioids. Overall, fewer participants randomized to XR-NTX were successfully initiated on treatment compared with those randomized to BUP-NX. Programs that did not use methadone or other medications during the detoxification process appeared to have higher XR-NTX induction rates, an important consideration for future research on the effectiveness and financial viability of providing XR-NTX in different treatment settings. Recent work indicates that alternative outpatient models of

XR-NTX initiation are feasible, which may both increase the number of patients who successfully initiate treatment and reduce the amount of inpatient/residential detoxification time necessary for those initiating treatment in such a setting.^{21,22} Additional studies are needed to explore the costs of implementing and providing OUD treatment as new medications are introduced and the role of primary care expands through more integrated behavioral health/physical health service delivery models.²³⁻²⁵ Surveying patients directly about the time and travel costs incurred to participate in treatment, as well as productivity benefits such as fewer days missed from work while receiving treatment, would support a more precise estimate of the net cost of these treatments for OUD from the patient (and, to some extent, employer and government) perspective.

Strengths and Limitations

Among the notable strengths of this study is that it is the first prospective cost analysis of XR-NTX and BUP-NX following inpatient detoxification treatment that is representative of diverse treatment sites and settings. The opportunity to work alongside a multisite

randomized controlled trial of XR-NTX and BUP-NX confers more precise (micro-) costing methods and results for all treatment and intervention components (eg, start-up, inpatient detoxification, medication induction, MM). The inclusion of patient time and travel costs expands the perspective of this analysis beyond the formal healthcare sector, where only the costs to providers and third-party payers are considered.

Limitations to this study include the lack of information on patient out-of-pocket and social services costs to inform a broader societal perspective on the costs of XR-NTX and BUP-NX. In addition, postdetoxification treatment services varied across sites, with some sites offering transition to formal residential treatment or outpatient programs in the same location as the inpatient detoxification program.

CONCLUSIONS

Providing XR-NTX and BUP-NX to patients receiving inpatient detoxification generates relatively modest additional costs to the healthcare sector for induction and MM visits. Improving access to evidence-based pharmacotherapy remains an important public health objective. Results of this analysis provide current practical information on the types of costs incurred by providers, payers, and patients in the implementation and provision of XR-NTX and BUP-NX for the treatment of OUDs across 8 unique inpatient detoxification sites. This information will be valuable to all stakeholders interested in expanding access to evidence-based OUD therapy. ■

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eAppendix Table 1. Cost Inputs (2015 US\$)

Cost Input		Unit Cost	Reference(s)
Personnel time, \$ per hour			
	Substance abuse and behavioral disorder counselor	21.23	1
	Mental health counselor	22.14	1
	Physician, general internal medicine	96.54	2
	Physician, trainee	29.47	1
	Registered nurse	34.70	1
	Nurse practitioner	50.30	1
	Physician assistant	49.08	1
	Mental health and substance abuse social worker	23.02	1
	Healthcare social workers	26.69	1
	Pharmacist	57.82	1
Medication costs, \$ per month ^a			
	XR-NTX, 380 mg	704	3
	BUP-NX		
	4 mg/1 mg	36	3
	8 mg/2 mg	65	3
Patient costs			
	Patient time, \$ per hour	7.25	4
	Transportation		
	Driving, \$ per mile	0.56	5
	Public, range \$ per 1 way	\$1.00 to \$2.75	6-8

BUP-NX indicates buprenorphine-naloxone; WAC, wholesale acquisition cost; XR-NTX, extended-release injectable naltrexone.

^aMedication costs valued at the WAC in scenario analysis for injectable XR-NTX, 380 mg (\$1309/injection); branded film BUP-NX, 4 mg/1 mg (\$5.09 per day); and branded film BUP-NX, 8 mg/2 mg (\$10.18 per day).⁹

eAppendix Table 2. Inpatient Detoxification Costs Per Patient (2015 US\$)^a

Cost Component	Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Mean (SD)	Median [IQR]
Inpatient detoxification costs, site-level										
Total annual cost of detoxification	\$6,847,225	\$2,442,831	\$1,255,847	\$1,599,722	\$2,234,775	\$3,821,888	\$5,208,253	\$2,322,640	\$3,216,648 (\$1,939,632)	\$2,382,736 [\$2,092,468]
Mean daily census	16	28	30	16	18	59	43	10	28 (16)	23 [17]
Total annual cost per detox patient	\$427,952	\$87,244	\$41,862	\$99,983	\$127,048	\$64,778	\$121,122	\$232,264	\$150,282 (\$125,801)	\$110,553 [\$71,725]
Mean daily cost per detox patient	\$1,172	\$239	\$115	\$274	\$348	\$177	\$332	\$636	\$412 (\$344)	\$303 [197]
Inpatient detoxification costs, participant-level										
Mean length of stay, days										
XR-NTX	6.4 (1.8)	14.6 (5.8)	5.5 (4.2)	6.8 (5.4)	6.3 (1.7)	6.8 (2.6)	10.5 (5.4)	3.0 (1.4)	8.0 (5.3)	6.0 [4.0]
BUP-NX	4.5 (1.3)	14.8 (5.8)	4.8 (1.1)	6.5 (6.0)	6.2 (1.1)	6.4 (1.6)	10.7 (4.0)	3.3 (1.7)	7.5 (5.1)	6.3 [3.0]
Mean detoxification episode cost										
XR-NTX	\$7491 (\$2112)	\$3481 (\$1398)	\$636 (\$484)	\$1856 (\$1483)	\$2201 (\$585)	\$1204 (\$466)	\$3481 (\$1805)	\$1908 (\$874)	\$3070 (\$2559)	\$2151 [\$2712]
BUP-NX	\$5313 (\$1576)	\$3532 (\$1392)	\$552 (\$126)	\$1785 (\$1632)	\$2166 (\$378)	\$1126 (\$286)	\$3551 (\$1344)	\$2107 (\$1052)	\$2663 (\$1913)	\$2088 [\$2277]

BUP-NX, buprenorphine-naloxone; IQR = interquartile range; XR-NTX, extended-release injectable naltrexone.

^aSDs reported in parentheses and IQRs in brackets. Mean daily census refers to the mean number of patients receiving detoxification services in a day.

eAppendix Table 3. Start-Up and Intervention Costs for XR-NTX and BUP-NX, Per Protocol Outcomes (2015 US\$)^a

Cost Component	Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H		Mean (SD)	Median [IQR]
Start-up costs, site level											
XR-NTX	\$980	\$853	\$509	\$2387	\$593	\$904	\$1580	\$251		\$1071 (\$682)	\$879 [\$558]
BUP-NX	\$800	\$750	\$448	\$1710	\$434	\$699	\$1305	\$91		\$780 (\$515)	\$725 [\$482]
Intervention costs, participant level											
XR-NTX											
	Detoxification	\$7960 (\$1795)	\$3861 (\$1233)	\$664 (\$529)	\$1868 (\$1534)	\$2225 (\$645)	\$1205 (\$456)	\$3394 (\$1827)	\$1749 (\$819)	\$2780 (\$2442)	\$2088 [\$2370]
	Provider	\$116 (\$62.18)	\$371 (\$65.50)	\$196 (\$98.92)	\$145 (\$55.63)	\$247 (\$71.49)	\$275 (\$156)	\$99.67 (\$48.46)	\$409 (\$160)	\$222 (\$132)	\$191 [\$198]
	Medication ^b	\$2464 (\$1621)	\$3114 (\$1246)	\$2216 (\$1583)	\$2631 (\$1506)	\$3200 (\$1398)	\$2870 (\$1802)	\$2933 (\$1551)	\$2816 (\$1376)	\$2778 (\$1530)	\$2816 [\$2816]
	Patient	\$127	\$141	\$309	\$89	\$181	\$268	\$197	\$329	\$191 (\$81)	\$181 [\$142]
	Total intervention cost, XR-NTX	\$10,667 (\$2438)	\$7487 (\$1882)	\$3385 (\$1694)	\$4733 (\$2197)	\$5853 (\$1668)	\$4618 (\$2094)	\$6623 (\$2442)	\$5303 (\$1688)	\$5970 (\$2893)	\$5999 [\$3468]
BUP-NX											
	Detoxification	\$5381 (\$1544)	\$3532 (\$1392)	\$555 (\$128)	\$1785 (\$1651)	\$2166 (\$382)	\$1087 (\$308)	\$3442 (\$1184)	\$2107 (\$1082)	\$2716 (\$1916)	\$2151 [\$2313]
	Provider	\$230 (\$125)	\$407 (\$130)	\$449 (\$220)	\$352 (\$124)	\$610 (\$211)	\$816 (\$556)	\$223 (\$102)	\$1136 (\$608)	\$461 (\$350)	\$386 [\$363]
	Medication ^c	\$587 (\$370)	\$432 (\$259)	\$590 (\$426)	\$527 (\$325)	\$535 (\$272)	\$396 (\$249)	\$455 (\$334)	\$488 (\$410)	\$510 (\$334)	\$496 [\$530]
	Patient	\$380	\$356	\$980	\$314	\$679	\$1019	\$632	\$1004	\$602 (\$363)	\$484 [\$443]
	Total intervention cost, BUP-NX	\$6577 (\$1695)	\$4727 (\$1557)	\$2573 (\$1030)	\$2977 (\$1882)	\$3938 (\$875)	\$3318 (\$1236)	\$4752 (\$1477)	\$4734 (\$1663)	\$4278 (\$1934)	\$3998 [\$2213]

BUP-NX indicates buprenorphine-naloxone; IQR, interquartile range; WAC, wholesale acquisition cost; XR-NTX, extended-release injectable naltrexone.

^aThe per protocol sample represents those participants that were successfully inducted onto BUP-NX and XR-NTX following randomization. Standard deviations in parentheses and IQR in brackets. Mean total intervention costs are based on detoxification costs and costs incurred during the intervention phase for medication induction and management. The cost of XR-NTX and BUP-NX medications is included here.

^bIn a sensitivity analyses, WAC estimates for XR-NTX were substituted resulting in mean and median costs increasing from \$2778 to \$4341 and \$2816 to \$5236, respectively.

^cIn sensitivity analyses, WAC estimates for branded film formulation of BUP-NX were substituted resulting in mean and median costs increasing from \$510 to \$2362 and \$496 to \$2275, respectively.

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