Cost-Effectiveness of Long-Term Outpatient Buprenorphine-Naloxone Treatment for Opioid Dependence in Primary Care

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BACKGROUND: Primary care physicians with appropriate training may prescribe buprenorphine-naloxone (bup/nx) to treat opioid dependence in US office-based settings, where many patients prefer to be treated. Bup/nx is off patent but not available as a generic.

OBJECTIVE: We evaluated the cost-effectiveness of long-term office-based bup/nx treatment for clinically stable opioid-dependent patients compared to no treatment.

DESIGN, SUBJECTS, AND INTERVENTION: A decision analytic model simulated a hypothetical cohort of clinically stable opioid-dependent individuals who have already completed 6 months of office-based bup/nx treatment. Data were from a published cohort study that collected treatment retention, opioid use, and costs for this population, and published quality-of-life weights. Uncertainties in estimated monthly costs and quality-of-life weights were evaluated in probabilistic sensitivity analyses, and the economic value of additional research to reduce these uncertainties was also evaluated.

MAIN MEASURES: Bup/nx, provider, and patient costs in 2010 US dollars, quality-adjusted life years (QALYs), and incremental cost-effectiveness (CE) ratios (\$/QALY); costs and QALYs are discounted at 3% annually.

KEY RESULTS: In the base case, office-based bup/nx for clinically stable patients has a CE ratio of \$35,100/QALY compared to no treatment after 24 months, with 64% probability of being < \$100,000/QALY in probabilistic sensitivity analysis. With a 50% bup/nx price reduction the CE ratio is \$23,000/QALY with 69% probability of being < \$100,000/QALY. Alternative quality-of-life weights result in CE ratios of \$138,000/QALY and \$90,600/QALY. The value of research to reduce quality-of-life uncertainties for 24-month results is \$6,400 per person eligible for treatment at the current bup/nx price and \$5,100 per person with a 50% bup/nx price reduction.

CONCLUSIONS: Office-based bup/nx for clinically stable patients may be a cost-effective alternative to no treatment at a threshold of \$100,000/QALY depending on assumptions about quality-of-life weights. Additional research about quality-of-life benefits and broader

health system and societal cost savings of bup/nx therapy is needed.

KEY WORDS: buprenorphine-naloxone; primary health care; cost-effectiveness; opioid substitution therapy.

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INTRODUCTION

In 2009 there were approximately 1.9 million individuals in the US with dependence on or abuse of opioid analgesics and 400,000 individuals with dependence on or abuse of heroin.¹ Long-term opioid agonist treatment with methadone or buprenorphine-naloxone (bup/nx) is the most effective treatment for opioid dependence.²

Buprenorphine-naloxone is a partial opioid antagonist that is an effective maintenance treatment for opioid dependence when compared to no treatment and equivalent in efficacy to moderate doses of methadone.^{3–8} As a result of the Drug Addiction Treatment Act of 2000, bup/nx can be prescribed by appropriately trained office-based physicians and dispensed at a pharmacy or on-site.⁹ Approximately 580,000 patients received bup/nx in 2009, many from non-specialist office-based physicians.^{10,11}

Lack of insurance reimbursement and limits on the duration of treatment are substantial barriers to the expansion of office-based bup/nx treatment.^{12,13} Although bup/nx is no longer patent protected in the US,¹⁴ there are no generic versions on the market, and the current cost of a 30-day prescription is at least seven times the medication cost of methadone.¹⁵ For many opioid-dependent patients, however, methadone maintenance is not a viable treatment option due to lack of access, the restrictiveness of daily methadone dosing, and social stigma.¹⁶ For these patients, office-based bup/nx is the only agonist maintenance treatment option, but the duration of their treatment may be limited by insurance coverage (unlike treatment for other chronic conditions) even though the need for maintenance treatment may be indefinite.^{12,17,18}

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Figure 2. Monthly probability of retention in treatment.

this same probability of drug use for simulated patients who drop out of bup/nx treatment in the Treatment cohort and for simulated patients in the No Treatment cohort, and vary this assumption in a sensitivity analysis (see below). For the 30% of the cohort, with a history of IDU,²⁵ we assumed that those who use drugs either out of treatment in the Treatment cohort or in the No Treatment cohort returned to injecting or continued to inject drugs; similarly those with a history of IDU who continued to use drugs while in treatment were assumed to be injecting drugs. Data from the observational cohort did not indicate differences between IDUs and non-IDUs in transition probabilities or probabilities of drug use; different costs and quality-of-life weights were used for IDUs and non-IDUs (see below).

Costs

Table 1 reports the monthly bup/nx, provider, and patient costs for office-based bup/nx treatment, based on data from the same prospective observational cohort.²⁵ Costs were calculated separately for patients with a history of IDU because prior research, including a study with this cohort, has demonstrated that patients whose primary opioid of abuse is heroin are more likely to use opioids while receiving bup/nx than patients whose primary opioid of abuse is opioid analgesics.^{28,30} Average daily bup/nx cost while on treatment was calculated as the total of all daily doses for all non-IDU or IDU patients multiplied by the unit cost per mg per dose and divided by the total days in treatment. This unit cost was based on the published price of \$1.90/mg for 2 mg buprenorphine/0.5 mg naloxone tablet and \$0.85/mg for 8 mg buprenorphine/2 mg naloxone tablet, adjusted for discounts frequently available to large public and private insurers using the published local discount for all Medicaid drugs (14% discount plus \$3.15 dispensing fee per 30-day prescription).¹⁵ All daily doses were calculated assuming the 8 mg buprenorphine/2 mg naloxone tablet could be split for a half-dose.

Table 1. Monthly Cost Model Inputs for Office-Based Buprenorphine/Naloxone Treatment (2010 US dollars)

	Non-IDU mean (SD)	IDU mean (SD)
Medication and provider costs		
Buprenorphine-naloxone*	354 (96)	390 (86)
Physician time	32 (26)	32 (26)
Nursing time†	17 (—)	17 (—)
Adjustment for missed visits	11 (6)	11 (6)
Overhead	28 (14)	29 (14)
Urine toxicology test cost‡	31 (28)	34 (34)
Liver function test cost§	5 (—)	5 (—)
Patient costs		
Travel time	13 (10)	13 (10)
Visit time	5 (2)	5 (2)
Transport cost	23 (33)	23 (33)

Non-IDU, non-intravenous drug user; IDU, intravenous drug user; SD, standard deviation

*\$396 (112) for non-IDUs and 418 (109) for IDUs without pill splitting

†\$8.50 twice monthly^{31,32}

‡\$28.75 per test³¹

§\$15.14⁴⁹ every 3 months

Provider costs include physician time, nurse time, and laboratory tests. Average monthly costs for physician time were calculated as the total of all patient visits multiplied by the cost of these visits and divided by the total patient months in treatment. Patients had two nurse visits per month and an average of 0.8 physician visits per month, which is consistent with clinical guidelines that recommend bi-weekly or monthly monitoring of stable patients.¹⁸ The durations of physician and nurse visits have been reported in a previous cost study.³¹ Following methods used in that cost study, we applied local labor and fringe benefit rates for physicians and nurses to the visit durations to determine visit costs, adding an additional 22% of the cost to account for time lost due to missed visits and a 46% overhead rate.^{31,32} A similar approach was used to calculate average monthly utilization and costs for urine toxicology tests from the study data, and we also assumed liver enzyme tests (alanine aminotransferase, aspartate aminotransferase) occurred every 3 months while in treatment.²⁵

Patient costs, including visit time, travel time, and monthly transportation costs, were derived from the previous cost study.³¹ Time costs were calculated by multiplying the duration of the visit and travel by the state minimum wage of \$8.25 per hour,³³ as more than half of the cohort reported not having full-time employment.²⁵

Quality-of-Life Weights

Quality-of-life weights for each health state are defined on a scale from 0 (death) to 1 (perfect health). Quality-of-life weights are from a societal perspective from a study conducted in the United Kingdom.³⁴ In this study, 22 members of a UK general population panel recruited to

complete internet surveys assessing health states using standard gamble procedures³⁵ evaluated descriptions of health states in and out of bup/nx treatment (Table 2).

Sensitivity Analyses

In one-way and two-way sensitivity analyses, we varied the following inputs. We reduced the cost of bup/nx by 20% to estimate the price reduction if there is one generic competitor, based on the price difference between branded and generic bup/nx,¹⁵ and by 50% to estimate the price reduction if there are multiple generic competitors.^{36,37} We extended the treatment duration to 60 months by projecting retention using a Weibull distribution fitted to data from the first 24 months ($\lambda=0.089$, $\gamma=0.721$), resulting in a median time in treatment of 24.3 months. We increased the probability of using drugs while in treatment to 50% and reduced the probability of using drugs while out of treatment and for those not in treatment to 50%. We examined results separately for individuals with and without a history of IDU.

Finally, we used alternative quality-of-life weights derived from the follow-up phase of a separate clinical trial evaluating the use of bup/nx for 14 days versus 12 weeks among opioid-dependent adolescents and young adults aged 15 to 21.^{38,39} In that study, at the 6-month follow-up appointment, 70 trial participants completed the EQ-5D quality-of-life questionnaire^{40,41} and reported current use of illicit drugs and of prescribed bup/nx. The EQ-5D responses were converted to quality-of-life weights representing the US societal perspective,⁴² and the resulting quality-of-life weights are reported in Table 2. There were insufficient data to separately report quality-of-life weights for non-IDU and IDU participants.

Table 2. Model Inputs for Quality-of-Life Weights

Inputs	Mean (SD)	Source
Base case		
In treatment, off drugs	0.867 (0.152)	³⁴
In treatment, on drugs, non-IDU	0.683 (0.204)	³⁴
In treatment, on drugs, IDU	0.633 (0.208)	³⁴
Out of treatment, off drugs	0.867 (0.152)	³⁴
Out of treatment, on drugs, non-IDU	0.678 (0.207)	³⁴
Out of treatment, on drugs, IDU	0.588 (0.212)	³⁴
Sensitivity analysis case		
In treatment, off drugs	0.856 (0.150)	Data analysis from ³⁹
In treatment, on drugs, non-IDU and IDU	0.876 (0.100)	Data analysis from ³⁹
Out of treatment, off drugs	0.856 (0.159)	Data analysis from ³⁹
Out of treatment, on drugs, non-IDU and IDU	0.806 (0.194)	Data analysis from ³⁹

SD, standard deviation; Non-IDU, non-intravenous drug user; IDU, intravenous drug user

For each one-way or two-way sensitivity analysis, we conducted probabilistic sensitivity analyses by running 10,000 Monte Carlo simulations that simultaneously varied all quality-of-life model inputs and all cost inputs except the price of bup/nx. For non-medication cost inputs we used lognormal distributions derived from the cohort data, and for quality of life inputs we used beta distributions derived from summary data (Table 2) using the method of moments.⁴³ Results are reported as the probability that the cost-effectiveness ratio of bup/nx treatment versus no treatment is below \$100,000 per QALY. We conducted expected value of partial perfect information (EVPPPI) analyses to describe the value of obtaining better quality data to reduce uncertainties in quality-of-life and non-medication cost inputs. The EVPPPIs represent the maximum value society should be willing to pay to eliminate all of the uncertainty about quality-of-life or non-medication cost model inputs.⁴³

RESULTS

Table 3 presents the base case and sensitivity analysis results. In the base case, the total cost of treatment over 24 months is \$7,700, and treatment results in 1.58 QALYs compared to 1.36 QALYs for no treatment, or an additional 0.22 QALYs. The cost-effectiveness ratio of office-based treatment in this clinically stable population is \$35,100/QALY. In probabilistic sensitivity analysis, there is a 64% probability that this cost-effectiveness ratio is less than \$100,000/QALY and a 55% probability that this cost-effectiveness ratio is less than \$50,000/QALY (Fig. 3).

Reducing the cost of bup/nx by 20% and 50% results in cost-effectiveness ratios of \$30,300/QALY and \$23,000/QALY, respectively. At current bup/nx costs, the cost-effectiveness ratio is \$35,200/QALY when the treatment duration is extended to 60 months, \$32,400/QALY when patient costs are excluded, \$39,300 when the analysis is limited to non-IDUs, and \$28,500/QALY when the analysis is limited to IDUs. The benefits of lower bup/nx costs in reducing (improving) cost-effectiveness ratios are similar to the base case, and the probability that the cost-effectiveness ratio is less than \$100,000/QALY is between 57% and 69%. When we varied the probability of using drugs while in treatment from 6% to 50%, the cost-effectiveness ratio was less than \$100,000 with 53% certainty. When we varied the probability of using drugs while out of treatment and for those not in treatment from 89% to 50%, the cost-effectiveness ratio was less than \$100,000 with 55% certainty.

Using the sensitivity analysis quality-of-life weights that do not distinguish between non-IDUs and IDUs, bup/nx treatment results in 1.69 QALYs compared to 1.64 QALYs,

Table 3. Cost Effectiveness of Office-Based Buprenorphine/Naloxone Treatment Compared to No Treatment

	Treatment cost (2010 US dollars)	Quality-adjusted life years (QALYs)	Incremental QALYs (compared to no treatment)	CE ratio (\$/QALY)*	Percent of probabilistic sensitivity analysis CE ratios < \$100,000/QALY
Base case					
No Treatment	0	1.36	—	—	—
Treatment					
Current bup/nx cost	7,700	1.58	0.22	35,100	64
20% bup/nx cost reduction	6,700	1.58	0.22	30,300	66
50% bup/nx cost reduction	5,100	1.58	0.22	23,000	69
60-month treatment duration					
No treatment	0	3.18	—	—	—
Treatment					
Current bup/nx cost	12,200	3.53	0.35	35,200	58
20% bup/nx cost reduction	10,500	3.53	0.35	30,300	60
50% bup/nx cost reduction	8,000	3.53	0.35	23,100	62
Sensitivity analysis quality-of-life weights					
No treatment	0	1.64	—	—	—
Treatment					
Current bup/nx cost	7,700	1.69	0.05	138,000	41
20% bup/nx cost reduction	6,700	1.69	0.05	119,000	41
50% bup/nx cost reduction	5,100	1.69	0.05	90,600	43
Probability in treatment on drugs=0.50 (0.06 in base case)					
No treatment	0	1.36	—	—	—
Treatment					
Current bup/nx cost	7,700	1.48	0.12	63,800	53
20% bup/nx cost reduction	6,700	1.48	0.12	55,000	54
50% bup/nx cost reduction	5,100	1.48	0.12	41,900	56
Probability off treatment or no treatment on drugs=0.50 (0.89 in base case)					
No treatment	0	1.53	—	—	—
Treatment					
Current bup/nx cost	7,700	1.65	0.12	65,700	55
20% bup/nx cost reduction	6,700	1.65	0.12	56,600	57
50% bup/nx cost reduction	5,100	1.65	0.12	43,100	60
Non-IDU only					
No treatment	0	1.41	—	—	—
Treatment					
Current bup/nx cost	7,600	1.60	0.19	39,300	57
20% bup/nx cost reduction	6,500	1.60	0.19	34,000	57
50% bup/nx cost reduction	5,000	1.60	0.19	25,900	59
IDU only					
No treatment	0	1.25	—	—	—
Treatment					
Current bup/nx cost	8,200	1.53	0.28	28,500	66
20% bup/nx cost reduction	7,000	1.53	0.28	24,500	66
50% bup/nx cost reduction	5,300	1.53	0.28	18,600	69

QALY, quality-adjusted life year; CE, cost-effectiveness; bup/nx, buprenorphine-naloxone; Non-IDU, non-intravenous drug user; IDU, intravenous drug user

*Cost-effectiveness ratios may not match previous columns due to rounding

or an additional 0.05 QALYs (compared to an additional 0.27 QALYs in the base case). The smaller QALY gain leads to higher (less attractive) cost-effectiveness ratios than in the base case: \$138,000/QALY at current bup/nx costs, \$119,000/QALY with a 20% bup/nx cost reduction, and \$90,600/QALY with a 50% bup/nx reduction. The probability that these cost-effectiveness ratios are less than \$100,000/QALY is between 41% and 43%; the probability that they are less than \$50,000/QALY is between 34% and 38%.

The EVPPI analyses confirmed the value of improving certainty in the quality-of-life weight estimates. Using the \$100,000/QALY threshold, the EVPPI for eliminating uncertainty about base case quality-of-life weights is \$6,400 per person eligible for 24-month office-based bup/nx treatment. At 20% and 50% reductions in bup/nx costs, the EVPPIs per

person are \$5,800 and \$5,100, respectively. In contrast, at each specified bup/nx cost level, the value from reducing uncertainty about the non-medication cost items was less than \$5 per person eligible for office-based bup/nx.

DISCUSSION

With the recent implementation of the Mental Health Parity and Addiction Equity Act of 2008,⁴⁴ more individuals will be able to obtain private and public health insurance coverage for substance abuse treatment on the same basis as medical treatment. Using cost-effectiveness methods routinely applied to medical treatments, our study found that extended office-based bup/nx treatment for clinically

Figure 3. Cost-effectiveness acceptability curve for office-based buprenorphine-naloxone treatment versus no treatment (base case).

stable patients compared to no treatment has a cost-effectiveness ratio of \$35,100/QALY and remains consistent as treatment duration is extended. The cost-effectiveness ratio is lower (more attractive) assuming a lower cost for bup/nx due to generic competition, but the impact is limited unless there are assumed to be multiple generic competitors. Currently, interventions with a cost-effectiveness ratio below \$100,000/QALY are considered to be good value in the US, although the threshold choice varies among decision makers. Many studies continue to use a threshold of \$50,000/QALY⁴⁵ from the mid-1990s, while others have argued for an even higher threshold of \$100,000/QALY to \$300,000/QALY despite the potential to encourage further increases in health care expenditures.^{22,23} Taking into account uncertainty in our model estimates for non-medication cost and quality-of-life, extended bup/nx maintenance treatment has a 64% chance of being cost-effective at a \$100,000/QALY threshold.

Three previous studies evaluated the cost-effectiveness of bup/nx compared to no treatment in populations with different costs, treatment durations, or sources of benefit, and found similar cost-effectiveness results. The UK study conducted for the National Institute for Clinical Excellence found bup/nx maintenance therapy to have a cost-effectiveness ratio of £26,429/QALY compared to no treatment from the national health system perspective in 2004, or \$60,400/QALY in 2010 US dollars.³⁴ The probability that the cost-effectiveness ratio was less than £65,000/QALY (approximately \$100,000/QALY) in this study was approximately 60%. The recent study conducted among US adolescents found that 12-week outpatient bup/nx compared to a 2-week bup/nx taper had a cost-effectiveness ratio of \$25,000/QALY (\$28,800/QALY in 2010 dollars) using a 12-month period of analysis when considering outpatient substance abuse treatment costs.³⁸ There was an 86% probability that the cost-

effectiveness ratio was less than \$100,000. An earlier study conducted in the US in 1998 found that if bup/nx increases access to opioid agonist treatment by 10%, it has a cost-effectiveness ratio less than \$45,000/QALY (\$70,700/QALY in 2010 US dollars), but this study only considered benefits attributable to reduced HIV transmission.⁴⁶

Our results are sensitive to quality-of-life weights, as indicated by the less attractive cost-effectiveness ratios when we used a different source for these weights. Further analysis using the EVPPi framework emphasizes the importance of conducting additional research to collect accurate data on quality of life on and off bup/nx treatment in a relevant population. Spending \$6,400 per eligible patient on quality of life research is economically justifiable according to this analysis, suggesting a rationale for a total budget of over \$735 million on this type of research assuming just 5% of the 2.3 million opioid-dependent individuals in the US are eligible for office-based bup/nx treatment. In fact, the actual cost of observational studies that collect quality-of-life data are much lower.

There are several limitations to the analysis. Data on treatment retention, drug use, and costs were from a single-site prospective cohort. Results may not be generalizable to other office-based setting or populations that were not previously involved in a clinical trial, although other observational studies have demonstrated similar levels of stability for selected patients receiving bup/nx in primary care.^{27,28,47,48} Costs and outcomes may not reflect current less-intensive patterns of care for clinically stable patients on bup/nx. Relapse to drug use after leaving office-based bup/nx treatment has not been documented, and drug use while in treatment was only 6% in this population; results were consistent when we varied these proportions in sensitivity analyses.

We were unable to consider the potential cost impact of office-based bup/tx treatment on the use of other health services; for example, in the UK successful treatment of opioid dependence is associated with reductions in the use of mental health services and increases in the use of primary care services.³⁴ We also did not include potential benefits from improved workforce participation and decreased criminal activity, although some of these benefits are presumed to be included in quality-of-life measures, nor from behavioral changes that decrease the risk of transmission of HIV and hepatitis C.²¹

The sources that we used for quality-of-life weights had small sample sizes and were not drawn from the same population that we modeled. The sensitivity analysis data have additional limitations in that they are derived from a young adult US population based on self-reported prescription bup/nx treatment that occurred outside of a trial protocol and were not independently documented. This may have contributed to the non-intuitive finding of a higher quality-of-life weight for those in treatment who continued to use drugs

than for those in treatment who did not use drugs. Nevertheless, these are the only quality-of-life weights we are aware of collected from bup/nx treatment patients in the US using a standard research technique (EQ-5D).

Importantly, this cost effectiveness analysis does not consider the costs and benefits of the initial 6-months of treatment. Patients who were eligible for and initiated long-term treatment in the observational cohort represented 32% of those who were randomized in the initial 6-month trial,²⁶ and this yield is likely to vary in different populations. If the costs are higher or benefits are lower for those who drop out of treatment, the cost-effectiveness ratio from the perspective of initiating treatment will likely be higher (less attractive). Finally, the results are not generalizable to a population for whom methadone maintenance would be an appropriate and available alternative.

Our findings demonstrate the potential economic value of office-based bup/nx for clinically stable opioid-dependent patients. We found that office-based bup/nx for these patients can be a cost-effective alternative to no treatment at an accepted threshold of \$100,000/QALY depending on assumptions about quality-of-life weights. Additional research about quality of life on and off bup/nx therapy can improve the certainty that the cost-effectiveness result meets this threshold. Further research about broader health system and societal cost savings associated with bup/nx treatment would also likely lead to lower cost-effectiveness ratio estimates.

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