

REVIEW

The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States

PAUL G. BARNETT,¹ GREGORY S. ZARIC² & MARGARET L. BRANDEAU³

¹Health Economics Resource Center, Veterans Affairs Palo Alto Health Care System, Menlo Park, CA and the Department of Health Research and Policy, Stanford University, Stanford, CA, ²Ivey School of Business, University of Western Ontario, London, Ontario, Canada & ³Department of Management Science and Engineering, Stanford University, Stanford, CA, USA

Abstract

Aims. To determine the cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States, particularly its effect on the HIV epidemic. **Design.** We developed a dynamic model to capture the effects of adding buprenorphine maintenance to the current opiate dependence treatment system. We evaluated incremental costs, including all health-care costs, and incremental effectiveness, measured as quality-adjusted life years (QALYs) of survival. We considered communities with HIV prevalence among injection drug users of 5% and 40%. Because no price has been set in the United States for a dose of buprenorphine, we considered three prices per dose: \$5, \$15, and \$30. **Findings.** If buprenorphine increases the number of individuals in maintenance treatment by 10%, but does not affect the number of individuals receiving methadone maintenance, the cost-effectiveness ratios for buprenorphine maintenance therapy are less than \$45 000 per QALY gained for all prices, in both the low-prevalence and high-prevalence communities. If the same number of individuals enter buprenorphine maintenance (10% of the number currently in methadone), but half are injection drug users newly entering maintenance and half are individuals who switched from methadone to buprenorphine, the cost-effectiveness ratios in both communities are less than \$45 000 per QALY gained for the \$5 and \$15 prices, and greater than \$65 000 per QALY gained for the \$30 price. **Conclusions.** At a price of \$5 or less per dose, buprenorphine maintenance is cost-effective under all scenarios we considered. At \$15 per dose, it is cost-effective if its adoption does not lead to a net decline in methadone use, or if a medium to high value is assigned to the years of life lived by injection drug users and those in maintenance therapy. At \$30 per dose, buprenorphine will be cost-effective only under the most optimistic modeling assumptions.

Introduction

Methadone maintenance has been demonstrated to be an effective treatment for opiate addiction

that reduces injection drug use and needle sharing^{1–4} and the overall mortality associated with abuse of opiates by injection.⁵ In previous

Correspondence to: Paul G. Barnett, Health Economics Resource Center, VA Palo Alto Health Care System, 795 Willow Rd (152 MPD), Menlo Park, CA 94025, USA. Tel: (650) 493 5000 ext. 2 2475; fax: (650) 617 2667; e-mail: paul.barnett@med.va.gov

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work, we determined that expansion of US methadone maintenance capacity would be a highly cost-effective health care intervention, with an incremental cost-effectiveness ratio of between \$8200 and \$10 900 per quality-adjusted life year (QALY) gained.⁶

Unfortunately, most individuals who could benefit from this treatment do not receive it. Of the estimated 600 000–800 000 heroin addicts in the United States only 115 000 are in methadone treatment.^{7,8} Eight states prohibit methadone treatment,⁸ and many health-care sponsors, including government Medicaid programs, do not include it as a covered benefit.

Buprenorphine has several advantages relative to methadone that make it a promising therapy for treatment of opiate dependence.⁹ Abrupt discontinuation of buprenorphine leads to withdrawal syndrome that is only mild to moderate.^{10,11} Also, although buprenorphine is a partial agonist of mu opiate receptors, at higher doses it acts as an antagonist, blocking its own effects. As a result, its dose-response curve reaches a plateau, limiting the drug's ability to cause respiratory depression.¹² This suggests that buprenorphine may be safer than methadone, which is associated with some risk from death due to overdose.¹³

A series of clinical trials have demonstrated that buprenorphine is as safe and effective as low-dose methadone for detoxification¹⁴ and maintenance of opiate addicts.^{15–19} Buprenorphine has been combined with the narcotic antagonist naloxone, a formulation that reduces the potential for abuse of buprenorphine by addicted individuals.²⁰ When taken sublingually, as indicated, the buprenorphine is absorbed but naloxone is not; when injected, however, the naloxone is absorbed, precipitating withdrawal in opiate-dependent individuals. A recent trial found this combination to be safe and effective.²¹

In France, buprenorphine is widely prescribed in primary care clinics as a maintenance therapy for opiate dependence: within a year of its introduction, 25 000 injection drug users were under treatment there.²² Currently it is estimated that some 60 000 drug users in France are on buprenorphine maintenance.²³ In the United States buprenorphine is not approved for maintenance therapy, nor is any oral formulation of the drug yet available. However, it has been proposed that buprenorphine be made available for US primary-care physicians to dispense as a maintenance treatment for opiate addiction.

Buprenorphine is under patent protection, and no price per dose has been set in the United States. A key question that will determine whether buprenorphine is adopted as a maintenance treatment in the United States is whether health-care payers will be willing to pay the price established by its manufacturer. Health-care payers will need to determine if the outcomes achieved by buprenorphine maintenance therapy justify its cost. This paper evaluates the incremental cost-effectiveness of buprenorphine maintenance therapy for injection drug users in the United States.

Methods

We developed a model to determine the effect of adding buprenorphine maintenance therapy to the US health-care system. We created a dynamic model to calculate the effect of treatment on the human immunodeficiency virus (HIV) epidemic, including the impact on sexual partners and needle-sharing contacts of those in treatment, and their contacts. We compared current health-care costs and outcomes to the costs and outcomes with the adoption of buprenorphine under different scenarios.

We divided the population into nine mutually exclusive groups ("compartments") based on HIV status (uninfected, asymptomatic HIV positive, AIDS) and drug use status (injection drug user, user in maintenance therapy and non-user). Individuals enter the population through maturation and leave via maturation or death. We calculated an all-cause mortality rate for each compartment, including the effect of AIDS, drug overdose and all other causes.

Transitions between compartments are described by a system of non-linear differential equations. One set of equations represents the rate of initiation of non-users into injection drug use, the transitions between untreated users and maintenance therapy and the rate at which individuals complete maintenance treatment to become non-users. A second set of equations governs the rate at which uninfected individuals contract HIV and the rate at which HIV-infected individuals develop AIDS. The equations that govern HIV transmission are dynamic. They reflect changes in HIV prevalence, as represented by the relative numbers of individuals in the compartments. A detailed description of the model is provided in our analysis of the cost-

Table 1. Key behavioral parameters used in dynamic model

	Untreated injection drug users	Individuals in methadone maintenance	Individuals in buprenorphine maintenance
Annual average number of injections			
Community with 5% HIV prevalence	200.0	40.0	53.3
Community with 40% HIV prevalence	225.0	45.0	59.9
Percentage of injections that are shared	20.0%	6.0%	7.2%
Annual number of new sex partners	3.5	3.5	3.5
Annual mortality rate from non-HIV causes	3.00%	1.13%	1.29%
Annual "graduation rate"	—	3.50%	2.78%

effectiveness of expanding methadone maintenance programs.²⁴

We considered the cost-effectiveness of buprenorphine in a community where HIV prevalence among injection drug users is 40% (such as New York City) and where it is 5% (a community such as Los Angeles); we refer to these as the high-prevalence and low-prevalence communities, respectively. We calibrated the model's parameters so that in the absence of buprenorphine treatment, its projections agreed with recent trends in the HIV epidemic. The model was not created to predict the future trends in the spread of HIV but, rather, to simulate the current spread of HIV, and the role of injection drug use in that spread. We calculated the effect of adding buprenorphine maintenance therapy on total health-care costs and total health-care outcomes over a 10-year time horizon. We chose a 10-year time horizon because it reflects many of the costs and benefits of treatment, but does not require us to make assumptions about the future direction of the epidemic and available treatments.

The model was developed to match our best information about behaviors of injection drug users, those in treatment and the general population, as well as the natural course of HIV infection. For example, the model assumes that the sexual partners of injection drug users are more likely themselves to be injection drug users. We assumed that individuals with AIDS are less likely to have sexual and needle-sharing partners than asymptomatic HIV-infected individuals. We assumed that untreated injection drug users are less likely than injection drug users in treatment to have access to anti-retroviral drugs, but more likely to use other health care services.

Values for key behavioral parameters used in the model are shown in Table 1. These parameters are based on an extensive review of the literature that is described in the technical description of our methadone model²⁴ and in a technical appendix to that paper which is available from the authors.

We assumed that injection drug users in the high-prevalence community would inject drugs at a slightly higher rate than those in the low-prevalence community. We estimated that individuals in methadone maintenance inject drugs 20% as often, and share needles 30% as often, as untreated injection drug users. We estimated that 3.5% of the individuals in methadone treatment in a given year will detoxify successfully from methadone and cease any further injection drug use.

Clinical trials have compared buprenorphine to methadone for short periods.¹⁵⁻¹⁹ Although no information exists on the long-term effects of buprenorphine, considerable information exists on the long-term effects of methadone. We assumed that the relative efficacy of buprenorphine versus methadone is the same over the long term as was observed in the short term. We modeled the long-term efficacy of buprenorphine treatment relative to the long-term effectiveness of methadone maintenance based on the difference between buprenorphine and methadone treatment efficacy observed in short-term trials. We used the results of a meta-analysis of trials comparing the effectiveness of buprenorphine to methadone.²⁵ This meta-analysis did not include trials that used low doses of buprenorphine. It determined that patients who received buprenorphine had 8.3% more positive urinalyses than patients receiving methadone and a 26% higher risk of terminating treatment.²⁵ We applied the

8.3% increment to the parameters characterizing risk behaviors while in maintenance treatment, including the average number of injections per year among individuals in treatment, the fractions of injections that are shared and the non-HIV death rate while in treatment. We applied the 26% higher risk of terminating treatment to reduce the annual "graduation rate" (the rate at which individuals terminate treatment and become abstinent). We assumed no reduction in sexual activity associated with maintenance therapy.

We applied the 8.3% higher rate of risk while in buprenorphine treatment as follows. We estimated that individuals in methadone maintenance inject only 20% as often as untreated injection drug users, and that individuals in buprenorphine maintenance inject 26.6% times as often ($0.266 = 1 - (1-0.20)(1-0.083)$). We estimated that untreated drug users share 20% of their injections, and that individuals in methadone maintenance share only 30% as often, or 6% of the time. We calculated that shared injections in buprenorphine maintenance occurs 35.8% as frequently as among untreated users ($0.358 = 1 - (1-0.3)(1-0.083)$), or 7.2% of the time. We estimated the annual death rate from causes other than HIV to be 3.0% among untreated users, and 1.13% among individuals in methadone maintenance. We estimated the annual non-HIV death rate among individuals in buprenorphine maintenance to be 1.29% ($0.0129 = 0.03 - (0.03-0.0113)(1-0.083)$).

We estimated that 3.5% of those in methadone maintenance successfully "graduate" from their programs each year; that is, detoxify from methadone and cease further injection drug use. This is based on a 65% annual rate of continuance in methadone maintenance, and an estimate that 90% who quit methadone maintenance each year return to regular injection drug use ($0.035 = (1-0.9)(1-0.65)$). We applied the 26% higher risk of terminating buprenorphine treatment by estimating an annual graduation rate of 2.78% ($0.0278 = 0.035/1.26$).

No price has been established in the United States for the take-home formulation of buprenorphine (buprenorphine compounded with naloxone). We estimated that the plausible cost of a daily dose of buprenorphine ranges from \$5 to \$30, based on the following considerations. In France, buprenorphine is sold in an 8-mg dose for 21.82 French francs (or \$US

3.45).²³ This is the lowest price that is likely to be set in the United States. All pharmaceuticals are purchased by the French national health plan, which gives it considerable market power in establishing the price. In addition, per capita spending for health care in France is smaller than in the United States, suggesting that French decision makers use a lower threshold for determining which interventions are cost-effective.

Our estimate of the highest plausible price (\$30) is based on the price charged in the United States for the analgesic formulation of buprenorphine. The drug is currently sold as 0.3 mg in a 1-ml ampoule at a wholesale cost of 10 for \$26.70 (26), which is equivalent to \$71.19 for an 8-mg dose. It is, however, much less expensive to compound an 8-mg dose in a single tablet than to compound the equivalent amount in 26 sterile ampoules. The cost of other analgesics is approximately one-fifth as much when they are sold as tablets as when they are sold in ampoules. The addition of naloxone, a generic product, is likely to add only a relatively small amount to the cost of the drug. This is borne about by the small extra cost when pentazocine is compounded with naloxone.

At \$5 per daily dose buprenorphine would cost \$1825 per year; at \$30 per dose the cost would be \$10 950 per year. We added to this cost \$3908 for the annual cost of urinalyses, physician evaluation and psychosocial interventions. This estimate is based on an evaluation of methadone programs which found that methadone maintenance therapy costs \$5250 per year.²⁷ The cost of methadone itself, about \$1 per dose, is \$365 per year; the balance, \$4885, represents the cost of distributing methadone from a specialized dispensary, physician evaluations, urinalyses and psychosocial interventions. If buprenorphine is dispensed as a take-home medication, then the cost of specialized dispensing will be saved. We assumed that the incremental cost of specialized dispensing is 20% of the remaining cost, or \$977. We estimated that dispensing staff account for 20% of the labor cost and space in a typical methadone clinic, with clerical, counseling, medical and administrative staff accounting for the other 80%.

The cost of the other activities, which are common to methadone maintenance and take-home buprenorphine, is the difference, \$3908 (i.e. \$4885 less \$977). Thus, we considered total annual buprenorphine maintenance cost of

\$5733, \$9383 and \$14 858, corresponding to daily dose costs of \$5, \$15 and \$30, respectively.

We incorporated all other health-care costs in our model. These are significant, as many injection drug users have severe medical and mental health problems and are at high risk for contracting HIV.^{28,29} Maintenance therapy reduces the risk of contracting HIV,^{1-4,30,31} and hence reduces the costs associated with treating HIV and acquired immunodeficiency syndrome (AIDS). On the other hand, injection drug users who enter treatment are usually screened for HIV, increasing the likelihood that if they are HIV infected they will receive expensive anti-retroviral drugs. We included not only the cost HIV medications and treatments for AIDS, but also the cost of treatment for all other illnesses, including other medical conditions that are co-morbid with injection drug use.

We used commonly accepted guidelines for evaluating new health-care interventions, which require that outcomes be expressed in terms of quality-adjusted life years (QALYs), that incremental costs and outcomes be discounted to their present value and that the analysis include not only the cost of the intervention, but all other health-care costs.³² All costs were adjusted to 1998 US dollars using the Consumer Price Index for all urban consumers.

We calculated the cumulative number of life years spent by the population in each health state over the 10-year time horizon. Life years were adjusted for the reduction in quality of life due to HIV infection, AIDS, injection drug use and time spent in maintenance treatment. Quality-adjusted life years (QALYs) are the recommended measure of outcome for health care cost-effectiveness studies.³² QALYs reflect both the quantity and the quality of life.³³ Life years of survival are adjusted for quality of life using a rating scale that varies from zero (representing death) to one (representing perfect health).

Quality adjustments for HIV and AIDS were based on values reported in the literature: 0.9 for asymptomatic HIV infection and 0.53 for AIDS.³⁴ No such assessments are yet available for substance abuse disorders. We used an adjustment of 0.9 for quality of life in maintenance treatment and 0.8 for the quality of life of an injection drug user. We used these values to represent the quality of life in these health states, including the associated burden of all co-morbid conditions except HIV and AIDS. (As a point of

comparison, quality adjustments for other conditions that limit activities include those for moderate angina (0.92), migraine (0.87), ulcer (0.84) and severe angina (0.82)³⁵). We multiplied the adjustments as appropriate to determine the quality of life in each population group. For example, for HIV infection and untreated injection drug use, we multiplied the adjustment for HIV (0.9) by the adjustment for drug use (0.8) to obtain a quality adjustment of 0.72. Costs and QALYs were discounted to present value at 3%.

We considered two scenarios for the impact of buprenorphine on opiate dependence treatment slots: in Scenario I, buprenorphine increased the number of individuals in maintenance treatment by 10% but did not affect the number of individuals receiving methadone maintenance treatment. It is possible that some individuals currently in methadone maintenance will prefer buprenorphine treatment, especially if it is prescribed in take-home doses, obviating the need for a daily visit to a methadone clinic. Thus, we also considered Scenario II, in which the same number of individuals entered buprenorphine maintenance as in Scenario I (10% of the number currently in methadone maintenance), but half were injection drug users newly entering maintenance and half were individuals who switched from methadone to buprenorphine. This case represents a 5% net expansion in treatment capacity.

Results

Results for Scenario I are shown in Table 2. In the low-prevalence community, a price of \$5 per buprenorphine dose yields an incremental cost-effectiveness ratio of \$14 000 per QALY gained; a price of \$15 per dose has a \$26 000 ratio; and a price of \$30 per dose has a \$44 200 ratio. In the high-prevalence community, the cost-effectiveness ratios are \$10 800, \$20 500 and \$35 000 for the \$5, \$15 and \$30 prices, respectively. Existing guidelines do not specify a cost-effectiveness threshold below which health care interventions must be below to be judged cost-effective; however, it is generally agreed that interventions that have a ratio of less than \$50 000 per QALY gained are cost-effective.³⁶

Results for Scenario II are also shown in Table 2. Since buprenorphine is more costly and less effective than methadone, the cost-effectiveness ratios are higher in this case than for Scenario I:

Table 2. Incremental cost–effectiveness ratios of buprenorphine maintenance treatment

	Buprenorphine cost per dose		
	\$5	\$15	\$30
Scenario I: Buprenorphine adoption results in 10% expansion in number of IDUs in maintenance and has no effect on number of IDUs in methadone maintenance			
Community with 5% HIV prevalence among IDUs			
Change in costs (\$US million)	3.8	7.1	12.1
Change in QALYs	274	274	274
Incremental cost–effectiveness ratio (\$US/QALY gained)	14 000	26 000	44 200
Community with 40% HIV prevalence among IDUs			
Change in costs (\$US million)	13.3	25.1	42.9
Change in QALYs	1226	1226	1226
Incremental cost–effectiveness ratio (\$US/QALY gained)	10 800	20 500	35 000
Scenario II: Buprenorphine adoption results in net 5% expansion in number of IDUs in maintenance and 5% decline in the number of methadone-maintained IDUs			
Community with 5% HIV prevalence among IDUs			
Change in costs (\$US million)	2.2	5.5	10.5
Change in QALYs	123	123	123
Incremental cost–effectiveness ratio (\$US/QALY gained)	17 700	44 500	84 700
Community with 40% HIV prevalence among IDUs			
Change in costs (\$US million)	7.9	19.7	37.4
Change in QALYs	561	561	561
Incremental cost–effectiveness ratio (\$US/QALY gained)	14 000	35 100	66 700

IDU = injection drug user.

in the low-prevalence community, the price of \$5 per buprenorphine dose has a cost–effectiveness ratio of \$17 700 per QALY gained, the \$15 per dose price has a \$44 500 ratio and the \$30 per dose price has a ratio of \$84 700. It is unlikely that buprenorphine would be adopted at the \$30 per dose price. In the high-prevalence community, the cost–effectiveness ratios are approximately 25% lower, but this effect is too small to favor adoption at the \$30 price.

Table 2 also reports the incremental change in cost and in QALYs associated with buprenorphine adoption. These values are relative to the 1 million individuals whose HIV and drug use status are modeled; any change in the size of the population modeled would simply change cost and outcomes by the same proportion, without affecting the cost–effectiveness ratios.

The Panel on Cost–effectiveness Analysis in Health and Medicine recommends the use of sensitivity analysis to determine where values of uncertain parameters could have a substantial impact on cost–effectiveness estimates.³² We therefore carried out sensitivity analysis to determine how our findings might change under different assumptions. To simplify the discussion, we present sensitivity results only for the low-prevalence community. This simplification is

conservative: the cost–effectiveness ratios for the low-prevalence community are 10–25% higher than those for the high-prevalence community.

We tested the sensitivity of our findings to variations in the effectiveness of buprenorphine relative to methadone. As noted earlier, a meta-analysis of trials found that buprenorphine-maintained subjects had 8.3% more positive urinalyses than methadone-maintained subjects; the 95% confidence interval surrounding this estimate was 2.7–14%.²⁵ The same analysis found that individuals in buprenorphine maintenance had 1.26 times the risk of discontinuing treatment, with a 95% confidence interval of 1.01–1.57 times the risk. These two dimensions of effectiveness are likely to be correlated; thus we conducted a two-way sensitivity analysis on these factors.

We determined the cost–effectiveness ratio with the effectiveness of buprenorphine set at the lower end of the confidence interval in both dimensions. We modeled the cost and outcomes if individuals in buprenorphine maintenance have 14% greater risk behaviors while in treatment and are 1.57 times less likely to complete treatment and become abstinent. In the low-prevalence community, the cost–effectiveness ratio was \$16 900 per QALY gained when

buprenorphine cost \$5 per dose, \$31 500 per QALY gained at \$15 per dose and \$54 000 per QALY gained at \$30 per dose. These ratios are approximately 20% greater than those in Table 2.

We also determined the cost-effectiveness ratio with buprenorphine effectiveness set at the high end of the confidence interval. Assuming that buprenorphine-maintained individuals have 2.7% greater risk behaviors and are 1.01 times less likely to complete treatment than individuals in methadone maintenance, the ratios reported in Table 2 decreased by about 11%. In the low-prevalence community, the cost-effectiveness ratio was \$12 300 per QALY gained when buprenorphine cost \$5 per dose, \$23 000 per QALY gained at \$15 per dose and \$39 800 per QALY gained at \$30 per dose.

The next sensitivity analysis considered the effect if buprenorphine were used more widely than we assumed in constructing our initial model. Using the parameters in our initial model, we considered the consequences if adoption of buprenorphine caused a 20% expansion in the number of individuals in maintenance treatment, rather than 10% as initially assumed. We also considered the case of the same number of individuals entering buprenorphine maintenance, with half representing new entrants and half representing individuals switching from methadone; that is, a 10% net increase in the number of individuals in maintenance treatment. In both cases, the cost-effectiveness ratios changed by less than 1% from the values reported in Table 2. Although buprenorphine costs more and is less effective than methadone (which increases its cost-effectiveness ratio), the inclusion of a larger number of individuals in maintenance results in greater marginal ability to prevent HIV transmission (which decreases the cost-effectiveness ratio).

The final set of sensitivity analyses considered different quality-of-life adjustments. The guidelines for cost-effectiveness analysis suggest that community ratings be used to assign quality adjustments for health states.³² Community valuation of health-care outcomes is recommended because cost-effectiveness analysis is a tool for assigning community health-care resources. We know of no work to establish the adjustments that should be used for substance use disorders.

The value of maintenance therapy depends on the quality of life associated with injection drug

use and the improvement in quality of life associated with entry into maintenance therapy. We constructed our model using a 0.8 quality adjustment for injection drug use and a 0.9 adjustment for maintenance therapy (i.e. a relatively high quality multiplier associated with injection drug use and a relatively modest 12.5% increment associated with maintenance therapy). In sensitivity analysis, we considered the effect of setting a high value for the benefit of treatment by using a quality adjustment for injection drug use of between 0.4 and 0.6, and assigning maintenance treatment a 25–50% higher adjustment (i.e. a lower quality multiplier associated with injection drug use than in the base case, and a higher increment associated with maintenance therapy). We also tested the effect of assigning low values to the benefit of treatment by using a quality adjustment for injection drug use between 0.2 and 0.4, and assigning maintenance treatment a value that was 10–25% higher. Finally, we considered the extreme case in which no value is assigned to the lives of injection drug users or to those in maintenance treatment (quality-adjustment multipliers of zero).

Table 3 presents the results of these sensitivity analyses under Scenario I, in which adoption of buprenorphine causes a 10% expansion in the number of individuals in maintenance treatment without reducing the number receiving methadone. At \$5 per dose, buprenorphine has a cost-effectiveness ratio of less than \$25 000 per QALY gained, regardless of the quality adjustment used. At \$15 per dose, buprenorphine has a cost-effectiveness ratio of less than \$45 000 per QALY gained, even when the analysis assigns a low quality of life to the lives of injection drug users and little additional value to maintenance. At \$30 per dose, the cost-effectiveness ratio exceeds \$50 000 per QALY gained unless a higher quality of life is assigned to injection drug use and maintenance therapy.

Table 4 presents the results of changes in quality adjustments under Scenario II, in which half of those who enter buprenorphine maintenance are from the untreated population and half are from methadone maintenance programs. At \$5 per dose, a lower value for the benefit of treatment raises the cost-effectiveness ratio to as high as \$40 000 per QALY gained. At \$15 per dose, treatment is below the \$50 000 per QALY threshold for cost-effectiveness ratios only if a medium or high value is assigned to treatment.

Table 3. Cost-effectiveness ratios (dollars per quality-adjusted life year gained): sensitivity analysis regarding quality-of-life adjustments. Community with 5% HIV prevalence among injection drug users, Scenario I—buprenorphine adoption causes no reduction in methadone treatment

Quality adjustment	Buprenorphine cost per dose		
	\$5	\$15	\$30
Base case: 0.8 for injection drug use, 12.5% greater for maintenance	14 000	26 000	44 200
High value assigned to benefit of treatment: 0.4–0.6 for injection drug use, 25–50% greater for maintenance	8500–14 500	15 900–27 100	27 000–46 000
Low value assigned to benefit of treatment: 0.2–0.4 for injection drug use, 10–25% greater for maintenance	14 500–20 600	27 100–38 500	46 000–65 200
No value assigned to years lived with injection drug use or maintenance treatment: 0.0 for injection drug use, 0% greater for maintenance	23 500	43 800	74 300

Table 4. Cost-effectiveness ratios (dollars per quality-adjusted life year gained): sensitivity analysis regarding quality-of-life adjustments. Community with 5% HIV prevalence among injection drug users, Scenario II—buprenorphine adoption causes 5% reduction in methadone treatment

Quality adjustment	Buprenorphine cost per dose		
	\$5	\$15	\$30
Base case: 0.8 for injection drug use, 12.5% greater for maintenance	17 700	44 500	84 700
High value assigned to benefit of treatment: 0.4–0.6 for injection drug use, 25–50% greater for maintenance	10 600–19 600	26 500–49 200	50 400–93 600
Low value assigned to benefit of treatment: 0.2–0.4 for injection drug use, 10–25% greater for maintenance	19 600–31 300	49 200–78 600	93 600–149 600
No value assigned to years lived with injection drug use or maintenance treatment: 0.0 for injection drug use, 0% greater for maintenance	40 000	99 800	190 000

At \$30 per dose, the cost-effectiveness ratios all exceed \$50 000 per QALY gained.

Discussion

Using our dynamic model and extrapolating the long-term effect of buprenorphine maintenance therapy from the results of short-term trials, we found that a \$5 per dose price for buprenorphine is cost-effective under all the scenarios we considered. At a price of \$15 per dose, buprenorphine maintenance therapy is cost-effective only if buprenorphine adoption does not lead to a net

decline in methadone use, or if decision makers assign medium to high value to the years of life lived by injection drug users and those in maintenance therapy. At \$30 per dose, buprenorphine maintenance therapy is cost-effective only under the most optimistic modeling assumptions.

A dynamic model is needed to estimate the effects of a treatment that reduces the spread of HIV. Much of the health benefits caused by the adoption of buprenorphine maintenance would be realized by non-drug users who avoid infec-

tion from HIV. We found that between 39% and 59% of the gain in quality-adjusted life years is accrued by individuals who are neither injection drug users nor in maintenance treatment. This benefit is so significant that a \$5 dose of buprenorphine will be considered cost-effective even if the benefits that are realized by drug users and individuals in maintenance are ignored (that is, with the assumption that both groups should be assigned a quality-of-life multiplier of zero).

In previous work, we determined that expansion of US methadone maintenance capacity would be a highly cost-effective health care intervention, with an incremental cost-effectiveness ratio of between \$8200 and \$10 900 per QALY gained. In this study, we found that buprenorphine, priced at \$5 per dose, has an incremental cost-effectiveness ratio of between \$10 800 and \$17 700 per QALY gained.

Expansion of methadone treatment is more cost-effective than adoption of buprenorphine under almost any of the scenarios we considered. However, regulatory constraints and community preferences have precluded an increase in methadone treatment capacity in the United States.⁸ Thus, even though buprenorphine maintenance is not the most cost-effective strategy for treating opiate addiction, decision makers may approve its adoption because it is feasible. Potential competition from methadone will probably constrain the ability of the buprenorphine manufacturer to set a price of more than \$5 per dose. It is possible that in the future buprenorphine will prove to be safer and more effective than methadone for certain types of patients; subsequent analysis may find a different cost-effectiveness ratio for care directed to these patients.

Reduction in opiate use reduces the cost of social service agencies and the criminal justice system. While these effects may be substantial, we did not include them in our analysis. Our goal was to take the perspective of a health-care sponsor who is considering whether to add buprenorphine maintenance therapy to its treatment formulary. We assumed that health-care decision makers would not include the reduced costs of government social service and criminal justice agencies as part of their economic criteria. In conducting this analysis, we assumed that buprenorphine should be evaluated like any other life-saving pharmaceutical intervention, us-

ing the cost-effectiveness methods that are applied routinely to medical care.³² By ignoring the other economic impacts, our estimate of the cost-effectiveness buprenorphine is conservative.

Our results suggest that if buprenorphine costs less than \$5 per dose (or, under certain conditions, less than \$15 per dose), it will be at least as cost-effective as other medical care interventions delivered to opiate-addicted individuals. For example, trimethoprim-sulfamethoxazole treatment of *Pneumocystis carinii* pneumonia in HIV-infected patients has a cost-effectiveness ratio of \$16 000 per QALY gained,³⁷ prophylaxis for *Mycobacterium avium* complex (MAC) in HIV-infected patients has a cost-effectiveness ratio of \$35 000–74 000 per QALY gained³⁷ and prophylaxis for cytomegalovirus retinitis has a ratio of \$160 000 per QALY gained.³⁸ The ratios we determined are also lower than those of many other health interventions not related to HIV.^{39–41}

Because buprenorphine is targeted to opiate addicts, policy makers may be tempted to apply a lower (more stringent) cost-effectiveness threshold to judge its cost-effectiveness. This is an inappropriate way to incorporate lower social preferences for the lives of drug users into the analysis: it does not consider that the non-drug-using population receives much of the benefit of maintenance treatment, via reduced spread of HIV. The appropriate way to incorporate social preferences about drug users into the analysis is via quality-of-life adjustments. Substance abuse researchers must place a high priority on the development of reliable quality-of-life adjustments for individuals with opiate dependence disorders and for those in maintenance treatment. Such quality adjustments will help determine the level of resources that should be assigned to treatment.

Factors other than cost-effectiveness considerations may influence those who decide whether to adopt substance abuse treatment innovations. Decisions about adoption of health-care interventions are influenced not only by the availability and cost of alternative treatments, but also by the political support for those affected by the disease being treated. Those who suffer from substance abuse disorders may be regarded as undeserving. Maintenance therapy carries an additional stigma. Some decision makers may not be influenced by evidence of cost-effectiveness, but instead be swayed by philosophical and

moral opposition to using an opioid to reduce craving for illicit opiates.

Our model considers the costs and benefits of maintenance therapy only over 10 years, rather than over the life-time of treated individuals. This choice of horizon is unlikely to bias our results. Bias might occur if buprenorphine were a time-limited intervention in which costs are incurred in the short term and benefits accrue over a life-time; however, maintenance therapy is a long-term treatment, and costs continue to be incurred and benefits continue to accrue.

We assumed that prescription of the buprenorphine/naloxone combination drug by primary care clinicians would have no effect on the rate at which individuals become addicted to opiates. While the formulation is designed to prevent abuse by opiate addicts, the abuse potential of this drug is small, but still untested.

We did not include the effect of cocaine injection practices. Individuals who inject cocaine are more likely than other opiate injectors to share injection equipment and engage in other high-risk behaviors,^{3,42} and may be less likely to reduce risky behavior while in maintenance treatment. The exclusion of cocaine injection practices from our model may have overstated the benefits of buprenorphine treatment.

Our analysis assumes that drug injectors share needles randomly with other drug injectors. Studies in several US cities have identified large social networks of injection drug users and have found that some drug injectors are much more likely than others to share needles with many other drug injectors (e.g. Suh *et al.*⁴³ and Neaigus *et al.*⁴⁴). If buprenorphine treatment reached injectors who are centrally located in such networks, then buprenorphine would be more cost-effective than we have estimated; conversely, if buprenorphine treatment reached drug injectors located on the periphery of such networks, then buprenorphine would be less cost-effective than we have estimated.

Our work is limited by the available information. Data are needed on the long-term effectiveness of buprenorphine and the effect of buprenorphine availability on the number of individuals in methadone treatment. Our analysis is also limited by lack of information about the types of individuals who will be enrolled in buprenorphine treatment and whether they would be easier or more difficult to treat than the opiate addicts enrolled in the trials that com-

pared buprenorphine to methadone. It is possible that buprenorphine will be primarily dispensed to individuals who are not sufficiently drug dependent to qualify for methadone maintenance. It is also possible that buprenorphine will be given to long-standing methadone users as a means of eventual detoxification, or to methadone treatment failures. The individuals who will receive buprenorphine, and its ultimate cost-effectiveness, will be strongly influenced by the regulations governing its uses as a maintenance therapy. Our analyses suggest, however, that buprenorphine will be a cost-effective treatment for opiate dependence in the United States, especially if the price per dose is \$5.

This same type of model can be used to understand the adoption of buprenorphine in other countries, but several changes would be needed. Analysts from other countries will need to consider that the cost of anti-retroviral drugs, health care and substance abuse treatment are likely to be lower than the United States. Behavioral parameters in the model may need to be modified to reflect different drug use and risk behaviors. Finally, health care payers will have different criteria for evaluating health care interventions; the US health-care system has one of the highest thresholds for judging the cost-effectiveness of health care interventions.

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