Review of Cost-Benefit and Cost-Effectiveness Literature for Methadone or Buprenorphine as a Treatment for Opiate Addiction

Revised: May 9, 2007

UMBC
AN HONORS UNIVERSITY IN MARYLAND

CENTER FOR HEALTH PROGRAM DEVELOPMENT AND MANAGEMENT

Acknowledgments

This is the second in a series of reports to the Baltimore City Health Department that aims to assist Baltimore in the evaluation of buprenorphine as a therapy for opioid addiction. This report was prepared by the Center for Health Program Development and Management (Center) at the University of Maryland, Baltimore County (www.chpdm.org). Support for this work comes from the Annie E. Casey Foundation.

Introduction

Burden of Disease/Extent of Treatment

In 2002, retired Senator Daniel Patrick Moynihan (D-NY)—notable for his distinguished career as both a public servant and social researcher—reflected about his role in setting national policies aimed at controlling the scourge of heroin addiction [1].

> While the riots and upheavals (of the late 60s) dissipated…heroin stayed, and the new administration had only the faintest idea of what, if anything, could be done. I certainly had none (p.26).

Moynihan was urban affairs advisor and a member of President Nixon's cabinet. His initial approach to the heroin problem was to address it from the supply side (i.e., via interdiction rather than treatment). Toward that end, in August of 1969, he traveled to France and Turkey to negotiate agreements that subsequently curtailed individual farm opium production in those two nations. Jubilant upon his return, he boasted of his accomplishments to economist and Secretary of State George P. Schultz. Schultz, wrote Moynihan, quickly discounted his strategy. The supply-side was at best only half of the story. If Moynihan was interested in reducing heroin use, he would have to find ways to limit demand. For the next 30 years Moynihan worked— typically against considerable resistance— to expand demand-side strategies, including methadone treatment programs, aimed at reducing heroin addiction.

November of 2007 will mark the 10-year anniversary of the release of a National Institutes of Health (NIH) Consensus Development Conference Statement that was specifically aimed at educating the medical community and the broader public regarding opiate addiction and treatment.[i] That conference remains an important milestone because the NIH-sponsored process represents what can be considered the nation's "supreme court" regarding controversial biomedical issues. In this case, a 12-member panel of experts (including experts in general and behavioral medicine) heard testimony from 25 other specialists before an audience of approximately 600 interested peers and other observers. As preparation for and in the wake of this public hearing, the panel also reviewed the extant literature, and ultimately crafted a consensus statement that was released for public review and comment. Within weeks of the conference, a final revised statement was released to reconcile all issues that came up during this intensive review and debate process. That released statement is strong and unequivocal:

> Opiate dependence is a brain-related medical disorder that can be effectively treated with significant benefits for the patient and society, and society must make a commitment to offer effective treatment for opiate dependence to all who need it….The unnecessary regulations of methadone maintenance therapy and other long-acting opiate agonist treatment programs should be reduced, and coverage for these programs should be a required benefit in public and private insurance programs.[i]

[i] See: consensus.nih.gov/1997/1998TreatOpiateAddiction108html.htm.

This statement should have been welcome and actionable news to policymakers nationwide, as opiate (principally heroin) addiction is a scourge that affects more than 80 million individuals around the world (Amato, 2005) including well over 1 million Americans [2-4].[ii] The impact of heroin addiction can be severe and even deadly— associated with poor health, premature death, and criminal behaviors that negatively impact the lives of those close to an addict, and those distant (be they victims of theft, or taxpayers supporting increased societal health care costs). Mortality for a heroin user is 13 times greater than for the general population, and the cumulative mortality for heroin use by age 50 is 53 percent [5]. Annual direct social costs of heroin use in France were recently estimated as follows [6]:

Healthcare:	186 million USD
Prevention and research:	116 million USD
Legal/judicial:	477 million USD
Loss of productivity:	744 million USD
Total	1.523 billion USD (1997 prices)

In the United States, the financial costs of heroin addiction are estimated at over 20 billion dollars per year [7, 8]:

Healthcare:	5.0 billion USD
Criminal activity:	5.2 billion USD
Social welfare:	0.1 billion USD
Loss of productivity:	11.6 billion USD
Total	21.9 billion USD (1996 prices)

Despite such information, approximately half of the state Medicaid programs do not support methadone treatment programs for adults [9][iii], and estimates indicate that well under 25 percent of heroin addicts actually have access to this type of care [4, 10-12].

Standard of Care

As indicated above, heroin addiction is almost universally accepted by experts as a cluster of biomedical disorders for which there are effective treatments. Most prominent among those treatments is the use of opioid maintenance therapy, principally methadone. Methadone is an opioid analogue that results in a less extreme high than heroin, while it simultaneously reduces withdrawal symptoms and blocks the biochemical activity of that illicit drug [13, 14]. The use of methadone is regarded as an integral component of what has been characterized as a "harm-minimization" approach to the treatment of heroin dependence. That approach has at least three components: 1) crime reduction, 2) reduction of the need for damaging heroin substitutes such as

[ii] For example, Stoller and Bigelow (2006) [3] note that the actual prevalence of heroin addiction is difficult to estimate, but that the Office of National Drug Control Policy estimates that in the US "hardcore" heroin addicts number between 750,000 and 1 million. Accordingly, it is quite reasonable to assume that undiagnosed heroin and non-hardcore opioid abusers bring that number well above the 1 million person mark.

[iii] See also: www.aatod.org/qa_medicare.html, data from 2005 (accessed 5/30/07) indicating 27 states permit some Medicaid reimbursement for methadone treatment.

benzodiazepines, and 3) allowing addicts to focus on aspects of their life besides the singular and often dangerous goal of obtaining more heroin [13]. While there remains some controversy regarding the ethics of providing opiates to addicts, the consensus is that such therapy is not only cost-effective from a societal perspective, but it also saves or greatly enhances the lives of those who are treated. Accordingly, two experts in the field recently wrote the following:

> The most unusual feature of methadone…maintenance treatment is the discrepancy between the significant body of evidence supporting its safety and effectiveness and its equally significant underutilization. [7] (p.6)

> The current methadone controversy is the most recent round in a policy struggle that has been going on since 1964, when the first program began….Many consider methadone treatment one of the really good ideas, if not great deeds in the history of the treatment of addiction…Methadone is not the panacea for our heroin problem….but neither is it the demon that some people would like to make it. [15] (pp.149, 158).

The latter quote notes the controversy and the reality that while methadone therapy is associated with measurable improvements in health and behavior (e.g., reductions in disease and crime), it is far from a perfect remedy. Additionally, methadone administration is constrained by a tightly regulated distribution system that requires specified clinical locations with limited connectivity to other aspects of our health care system [16]. These limitations underscore the need for other modes of therapy. Buprenorphine is one of these modalities.

Like methadone, buprenorphine is an opioid agonist (receptor activator). However, in contrast to methadone, buprenorphine can be used with lower abuse and overdose potential. This increased safety exists because at increased doses, buprenorphine acts as an opioid antagonist, thereby reducing the physiologic response associated with the heroin high [14, 17]. Use of buprenorphine is not as widespread in the United States as methadone because it is newer and more expensive. It nevertheless offers an alternative to methadone with some notable advantages. These advantages are tied to the antagonistic properties of the drug, which have led federal regulators to classify buprenorphine as a substance that can be prescribed in standard outpatient settings rather than in the more controlled network of methadone clinics. Additionally, buprenorphine's reduced toxicity allows clinicians to consider prescribing regimens that include alternate day administration and/or "take home" doses of the medication [18].

Purpose

The purpose of this report is to review existing and the most up-to-date scientific literature regarding the cost-benefit or cost-effectiveness of opioid agonist therapy to address heroin addiction. Literature on both methadone and buprenorphine is reviewed here with the *a priori* hypothesis that these treatments are equivalent in their efficacy, even as buprenorphine may currently be more expensive then methadone. Cost-benefit analysis considers the overall societal costs of a treatment compared to the overall benefits obtained. Cost-effectiveness considers the costs necessary to achieve a specified output, such as an added quality adjusted life year

(QALY). Cost-effectiveness is frequently used to compare two (or more) alternatives, like methadone and buprenorphine treatment, to determine which one achieves the same outcome at the lowest price [19].

Review of buprenorphine as an alternative to methadone for the treatment of heroin addiction is especially important to urban centers in the United States where heroin addiction is concentrated. Furthermore, expanding therapeutic options is imperative, given the large gap between those who are addicts and those who actually receive treatment. As indicated in the introduction of this report, this unmet need for opioid maintenance therapy is on the order of 700,000 Americans [2-4, 10-12].

Baltimore City appears to be no exception. Despite the fact that Maryland Medicaid covers methadone maintenance therapy, a recent study prepared by the Center found that in Baltimore City and the rest of state, during fiscal years 2003 to 2005, more than 35 percent of opioid dependents—many of whom had continuous Medicaid coverage during those years—were not enrolled in methadone or any other pharmacologic treatment programs. This suggests that there is an opportunity for expanding the availability and penetration of methadone or other maintenance therapies in Maryland. The review below is designed to survey the existing literature on the cost-benefit and cost-effectiveness of methadone and buprenorphine.

Methods

Standard on-line library databases were searched including Econlit, PsycInfo, Pubmed, Academic Search Premiere, Cochrane Databases, and Medline. Keywords used were "methadone" or "buprenorphine"; and "cost-effectiveness" or "cost-benefit" including an exploded list for these latter two keywords of associated Medical Subject Heading terms available at Pubmed (www.pubmed.gov). These database searches, conducted in February of 2007, identified over 100 potentially relevant articles. All identified titles and abstracts were reviewed to isolate those indicating content corresponding to the generation of new knowledge regarding the CB or CE of either methadone, buprenorphine, or both as treatment for opioid abuse or dependence. Particular emphasis was given to empirical studies, meta-analyses or other systematic reviews, and novel econometric modeling studies. Additionally, based on the premise that methadone represents the current 'gold-standard' regarding opioid maintenance therapy, articles that directly compared buprenorphine to methadone were reviewed, even if they did not contain specific CB or CE analyses. A few articles focusing on the efficacy of buprenorphine alone were also retained given that expansion of such treatment is currently a prominent issue in the addiction treatment debate and one central to the genesis of this study.

Findings

From the original list of approximately 100 articles, more than 30 were reviewed in their entirety, and 13 of those were considered to add new knowledge regarding the cost-benefit or cost-effectiveness of methadone or buprenorphine. **Table 1** summarizes those 13 articles, the earliest of which was published in 1993, and the text below provides a description of their

approach, limitations, and findings. For simplicity, and to appreciate the evolution of the field, these studies are reviewed in chronological order.

The oldest article reviewed here was by Korsten and colleagues [20] and is a comparative efficacy trial, meaning that it contrasted the treatment impact of buprenorphine versus that of methadone in a randomized control trial. The study was small (n=140) and only 73 of the participants completed the protocol. A notable feature of this protocol was the double-dummy design, which required all subjects to take two dose—one true (methadone or buprenorphine), the other a placebo. This aspect of the trial was necessary because methadone is typically taken orally, whereas buprenorphine is taken sublingually.[iv] The trial also involved administration of low and high doses of both treatment agents. Outcome variables favored methadone over buprenorphine across measures, though higher doses of buprenorphine approached the efficacy of methadone on some of these measures. For example, among the 73 study completers, illicit heroin expenditures were 90-95 USD per month across both groups; whereas in the low dose buprenorphine group, they were 260 USD per month. Prior to the start of the trial, heroin expenditures were nearly 2,000 USD per person per month. These results, at least in quasi-experimental fashion, underscore a point that is quite consistent across studies: neither methadone nor buprenorphine is a perfect remedy for heroin addiction, but if administered correctly, illicit heroin use can be greatly attenuated by either agent.

In 2001, prominent mental health and substance abuse researcher Robert Rosenheck was lead author on a modeling study that aimed to address costs associated with office-based buprenorphine and compare those costs to clinic-based methadone [11], the latter being the mandated and separate treatment standard for opioid maintenance therapy in the United States. Using available data from other sources, Rosenheck and his colleague calculated costs of methadone and buprenorphine therapy over the initial year and subsequent years of treatment. Parameters they considered when estimating costs were: direct medical expenses (medication, dispensing, counseling, facility, and toxicology screening) and patient costs (specifically travel costs to the clinic). They based their analysis on two key assumptions. First, they anticipated that buprenorphine would soon be widely available as an alternative treatment for opioid addiction, and second, their reading of the data and the scientific literature led them to conclude:

> The major advantage of buprenorphine/naloxone,[v] thus, is not greater pharmacologic efficacy, but rather in its greater safety and acceptability to society as a medication that can be used in office practice (p. 254).

Accordingly, these authors had moved from the question of comparative effectiveness to comparative cost. This study, however, is neither a cost-benefit nor cost-effectiveness analysis as it does not look at outcomes directly. Rather, it models the cost of continuous therapy using one or the other pharmacologic interventions, thereby implying that the treatments are similar in their duration and benefits profile. In modeling the costs of each mode of therapy, they do carry out sensitivity analysis of their cost estimates by considering a range of input parameters (e.g.,

[iv] By placing it under the tongue and allowing it to dissolve.
[v] The combination therapy known by the trade name Suboxone. Naxolone is an opioid antagonist.

buprenorphine costs are varied from 4 to 8 USD per 12mg dose;[vi] counseling services levels are also varied from low and high levels). The summary calculations they present suggest that buprenorphine therapy is associated with similar overall clinical costs as methadone. However, when patient transportation costs are factored in, buprenorphine therapy is actually less expensive because standard outpatient care facilities are far more prevalent than methadone clinics.

While the modeling put forth by Rosenheck and Kosten is encouraging regarding the true overall costs of buprenorphine, it is hypothetical and based on some slightly tenuous assumptions regarding the comparative needs of those on buprenorphine and those alternatively on methadone. Most notably, they assume that buprenorphine recipients will require less frequent counseling and toxicology services than most methadone recipients, presumptions that are supported in recent reports [21], but which remain speculative in the absence of further empirical study.

Finally, it is worth noting that Rosenheck and Kosten discuss an important concept not always addressed in drug trial studies: the issue that clusters of patients may respond differently to different types of therapy. Specifically, they note that there are at least three types of opioid addicts to consider when evaluating the relative efficacy of methadone and buprenorphine: 1) high utilizers, requiring the most intensive treatment—perhaps daily administration of methadone with regular therapy, 2) low utilizers of heroin who, in the absence office-based treatment options, remain "in the closet" addicts, and 3) pain treatment patients who have serious addiction to opioids such as Oxycontin, but remain "in the closet" like low utilizers of heroin. The authors argue that the latter two groups may be most responsive to buprenorphine therapy, making it most cost-effective for these groups.

Similar to the above study, Barnett and colleagues (2001) also developed a model to consider the comparative costs of methadone and buprenorphine therapies, this time with particular emphasis on how these treatments affect the HIV epidemic [10]. Cost-effectiveness modeling was done for hypothetical communities with low (10 percent) or high (40 percent) HIV rates, and quality adjusted life year (QALY) calculations included weighting based on the presence and level of HIV infection (e.g., a life year was down-graded by a factor of 0.53 for someone with AIDS, but only by a factor of 0.9 for asymptomatic HIV). Additional sensitivity analyses were conducted to consider the effects for variable rates of: 1) needle sharing, 2) multiple sex partners, 3) mortality from HIV, 4) graduation from therapy, and 5) buprenorphine costs.

Cost-effectiveness analysis across various combinations of these parameters indicated that nearly all scenarios with methadone were cost-effective, using the broadly accepted threshold of 50,000 USD per added QALY. Buprenorphine also surpassed that same cost-effectiveness threshold except in scenarios where the drug was estimated at a very high price (30 USD per dose), and when the model assumed that increasing the proportion of those in treatment by 10 percent would involve reducing those on methadone by 5 percent (i.e., half of all new buprenorphine users would be those who previously were on methadone— a relatively extreme level of substitution).

[vi] The drug Methadone costs less than 1 USD per day.

These results led Barnett and colleagues to conclude that methadone was always more cost-effective than buprenorphine, but that given regulatory and political constraints, buprenorphine represents a viable and only slightly more costly alternative. At the extremes, in a high HIV prevalence community where buprenorphine was relatively inexpensive (5 USD per dose) and the expansion resulted in the exclusive recruitment of previously untreated individuals into therapy, the cost-effectiveness of buprenorphine was 10,800 USD per QALY. By comparison, this ratio increased nearly eight-fold if buprenorphine was assumed to be very costly (30 USD per dose), and if half of those treated with this newer agent were drawn away from methadone maintenance therapy.

Barnett et al.'s work elicited swift praise and criticism from other experts in the field. All noted that in addition to the burden of HIV, more extensive analyses should consider broader societal costs associated with heroin addiction (especially crime, but also employment costs) [22-24]. Regarding methadone's dominance over buprenorphine, Sindelar [24] was particularly blunt:

> Why then do we not significantly expand the provision of methadone maintenance? …[because] Politics matter. (p.1517-8)

Lavignasse and colleagues (2002) carried out a pre/post buprenorphine treatment study with a convenience sample of 690 individuals [6]. Subject retention and response rate were both high at 72 and 89 percent, respectively. Individuals were followed for six months, and outcomes were favorable, though not subject to validation by any control group. For example, heroin use rates declined (from 75 to 14 percent), as did arrest rates (from 20 to 9 percent). The sensation of being a threat to one's principal partner declined markedly as well (from 57 to 17 percent).

In 2003, Healy and colleagues conducted yet another pre/post treatment experiment, this time with methadone prescriptions in one of three settings: 1) primary care or community health centers, 2) inpatient drug units, or 3) residential rehabilitation centers [25]. They used treatment costs per crime avoided as the variable of interest. Multivariate Poisson modeling was used to calculate the cost per crimes avoided and to account for the skewing in the crime count distribution. The study sample was composed of over 1,000 hardcore (>60 percent injectors, >26 percent incarceration history, <15 percent wage earners), principally male (70 percent) heroin users residing in the United Kingdom. Although the study was said to include four- to five-year follow-ups, data reported in this publication were only for baseline and six-month time periods. Regression modeling indicated that the treatment cost associated with incremental crime reduction ranged from approximately 192 to 322 USD (the latter number calculated with outliers removed). Whereas mean crime counts were 49.9 before and 13.1 after treatment, median counts were 2 and 0, respectively, reflecting the skewed nature of these crime[vii] statistics and the infrequency of criminal activity even in a "hardcore" population entering treatment. As to the significance of these crime reduction costs, the authors demur from making their own conclusions:

[vii] Total of self-reported offenses ranging from drug crimes to burglary and prostitution.

> The onus is on public decision-makers to decide whether the predicted reductions in crime are worth the opportunity costs of investing resources (p.134)

As an introduction to their randomized trial of buprenorphine versus methadone, Doran et al. (2003) noted that prior data and literature revealed benefits to cost ratios for treatment in outpatient methadone clinics in excess of 11 [26]. They furthermore observed that several clinical trials indicated that buprenorphine was either comparable in efficacy to methadone, or only slightly inferior when used at lower doses. From those optimistic appraisals, they described their randomized clinical trial of outpatient-based buprenorphine and methadone. Between the years of 1996 and 1998, they enrolled 405 adult heroin addicts across three separate clinics in Australia and randomized them to buprenorphine or methadone treatment groups. Total clinical treatment costs (staff time, medications, and facility expenses) were estimated by empirical chart review matched to standardized fees. These chart reviews were conducted on half of the sample, and then extrapolated to the remaining half. The primary outcome variable was heroin-free days one month prior, and six months post the initiation of therapy.

Overall results indicated that treatment costs were only marginally higher for the buprenorphine group, whereas the number of heroin-free days at month six was marginally reduced for that group. Accordingly, incremental cost-effectiveness ratios for methadone and buprenorphine overlapped, suggesting that the treatments were comparable, at least with regards to provider treatment costs. Unfortunately, however, there are some careless aspects to this report, most of which were described by Capelhorn and Deeks [27]. For example, the write-up refers to a placebo group when there seems to be none; it misreports a critical probability by a factor of 10; and it inappropriately uses nonparametric statistical tests, thereby giving the false impression that methadone is *not* slightly superior to buprenorphine. Capelhorn and Deeks also noted that the censuring of 277 subjects who were lost to follow-up inappropriately biased the results slightly in favor of buprenorphine [27]. Despite these problems, this study is distinguished as one of the few to carry out a cost-effectiveness analysis using a randomized control design, and the results indicate considerable overlap between methadone and buprenorphine.

In 2004, Gowing et al. published one of several Cochrane database reviews, focusing on buprenorphine or methadone treatment for heroin addiction [28]. The Cochrane reviews are prominent and highly respected synthetic reports coalescing and analyzing clinical trial results for wide dissemination (see www.cochrane.org). This particular review is one of several that consider the acute detoxification phase of opioid addiction treatment (i.e., days 0-20 of treatment). This review identified 14 reasonable to high-quality randomized control and four non-randomized trials that provided information regarding buprenorphine as a detoxification therapy. Without reference to costs, the findings of these 18 studies were said to indicate that buprenorphine is superior to both methadone and clonidine[viii] in the management of withdrawal symptoms that are typical of the detoxification phase. Buprenorphine's superiority over clonidine was said to be especially evident.

In 2005, Amato and colleagues published a Cochrane-style review of 52 individual studies—10 of which were controlled studies—corresponding to over 12,000 participants [5]. Thirteen of the

[viii] An antihypertensive agent.

studies (total n=2,544) compared buprenorphine to a placebo or to other opioid maintenance drugs. The remaining studies isolated methadone at various doses or other less commonly utilized maintenance drugs (i.e., LAAM and heroin). Across all studies, outcome variables included: treatment retention, illicit heroin use, mortality, and crime statistics. Five studies from that review indicated that high doses of methadone are slightly more likely to result in treatment retention than high doses of buprenorphine (52 vs. 41 percent), and the same number demonstrate that buprenorphine is significantly superior to placebos, with retention rates in the 61-55 percent range versus those in the 41-38 percent range. Mortality statistics across two studies and crime statistics across three studies (both for methadone only) favored the treatment over a "waiting list" status, but the differences were not statistically significant. As mortality rates across all 14 studies in that category were 6 percent or less, the absence of significant findings may well be tied to statistical power constraints.

In 2005, an Australian study was conducted that was said to be one of the first cost-effectiveness analyses of buprenorphine that included broad societal impacts (i.e., crime cost estimates based on medical bills associated with assaults, and depreciated values of damaged property) [29]. Unfortunately, the sample size was very modest (n=139) and the dropout rate was very high (50 percent). Still, the design was at least randomized, though not blinded, and they did use QALYs as an outcome indicator. Their overall result favored buprenorphine; however, it favored methadone if the crime data was eliminated and if outliers were culled from the analysis. Outside of the cost-effectiveness analysis, an intent-to-treat analysis did not differentiate the number of heroin-free days over the 12 month trial (225 and 222 for methadone and buprenorphine, respectively). These numbers not only indicate comparable efficacy, but they also demonstrate that these treatment effects fall well shy of yielding complete (365 days) abstinence from heroin.

Simoens et al. (2006) conducted what they referred to as a "comprehensive review" of cost-effectiveness and cost-benefit literature from 1995 to 2005, and then they carried out a meta-analysis using 12 qualifying studies (many non-overlapping with the ones described in this report) [30]. A compilation of point estimates across these studies found that incremental cost-effectiveness ratios for opioid maintenance of various types ranged from $3,451 to $9,103 (1996 USD) per additional QALY. Both US- and UK-based studies were also compiled, indicating that methadone treatment demonstrates benefit to cost ratios on the order of 3 to 15. Evidence regarding methadone versus buprenorphine was summarized as "equivocal" since their review contradicted Rosenheck and Kosten's calculations that demonstrated the superiority of buprenorphine [11]. Only four studies were noted to consider full societal perspectives (e.g., crime, health cost, patient costs such as transport, and QALYs). No doubt also inspired by the discourse of Rosenheck and Kosten, Simoens and colleagues also noted that economic analysis so far has:

> …failed to identify the sub-groups of subjects and the conditions under which community maintenance for opiate dependence has the highest economic value. (p. 38)

Shannahan and colleagues (2006) published two reports focusing on buprenorphine: one relating to detoxification efficacy [31], and the other to maintenance treatment cost and outcomes [32]. Both studies were conducted in Australia.

The detoxification study involved a clinical trial of five modes of therapy: 1) sedation, 2) anesthesia, 3) buprenorphine, 4) inpatient clonidine, and 5) outpatient clonidine. Each treatment group contained at least 24 participants, and outcome variables were heroin abstinence and entry into post-detoxification programs. Costs were considered from the provider perspective only because client care was completely subsidized. Tallied costs included those pertaining to staff time, medications, supplies, and facility space. Buprenorphine therapy dominated all others as it demonstrated the highest incremental cost-effectiveness ratios for both outcomes. Its performance regarding tracking to post-detoxification maintenance programs was particularly impressive at 65 percent, higher than all others except the sedation technique (68 percent), but at a quarter of that technique's cost (320 vs. 1,300 USD). The rate of successful transition to maintenance therapy for buprenorphine (65 percent) was apparent even as only 12 percent of those treated remained heroin-free during the entire detoxification period: a clear indication that the opportunity for on-going treatment is not necessarily tied to perfect or near perfect abstinence.

Shanahan et al.'s other report summarized a naturalistic pre/post buprenorphine or methadone (not differentiated) treatment study that followed 745[ix] participants for 12 months and assessed their treatment costs in comparison to outcomes, including self-reported heroin-free days and criminal activity.[x] Mean overall treatment costs were approximately 4,236 USD, which yielded a 53 percent reduction in criminal activity, and an increase in self-reports of heroin abstinence from 2 to 53 percent. The abstinence rate of 53 percent represents the "half empty, half full" characteristic of opioid maintenance treatment. On the one hand, treatment results in large gains; on the other hand, heroin addiction is typically a "chronic relapsing disorder" [5] for which there is currently no universal or perfect treatment.

In their maintenance treatment study, Shanahan et al. provide a useful juxtaposition of opioid treatment costs to the costs of other medical interventions. These numbers clearly suggest that opioid maintenance therapy is reasonably priced in comparison to other common medical or social interventions:

Annual treatment costs (USD)	
Opioid maintenance therapy:	4,236
Overall health care costs per capita:	2,140
Care post-stroke:	3,205
Schizophrenia case management:	16,965
12 month incarceration:	44,200

Finally, a 2006 Cochrane database review represents a minor update of a meta-analysis from 2003 [33]. This was a systematic review of 13 qualifying studies comparing buprenorphine to

[ix] Complete data was collected on 596 participants.
[x] Daily costs for methadone and buprenorphine treatment were derived from secondary sources, and were approximately 7 and 11 USD, respectively.

methadone at low and high doses for both drugs. Most studies used retention and urinalysis results as principal outcome variables; only a single study considered crime statistics. The duration of all studies combined ranged from 6 to 52 weeks. The conclusions of this review are consistent with results noted previously in this paper: buprenorphine is superior to placebos, but slightly inferior to methadone. The authors do not describe cost information, but they do note that they found the general quality of the studies they reviewed to be adequate or better.

Conclusions

The 13 studies reviewed above indicate that methadone and buprenorphine are cost-effective treatments for heroin or other opioid addiction, and that methadone is typically the most cost-effective therapy of these two. However, given that 1) there is a political and regulatory structure that surrounds methadone distribution in the United States, and 2) some individuals might be unable, unwilling, or unresponsive to methadone clinical treatment, buprenorphine—especially at higher doses—seems to present a very viable alternative to methadone.

This overview of scholarly literature on the cost-effectiveness and cost-benefits associated with buprenorphine or methadone treatment yielded a very modest number of relevant studies. Still, 4 of the 13 reports identified were themselves comprehensive reviews of previous work such that the aggregate information summarized here can be considered a fairly robust and up-to-date[xi] review of the academic literature on the subject.

Of the 13 studies reviewed, 2 focused on the early and acute stage of addiction therapy referred to as detoxification; the remaining 11 focused on the long-term, post-detoxification phase of therapy know as maintenance therapy. The two detoxification studies appear to unequivocally endorse buprenorphine as a cost-effective alternative to methadone or clonidine therapy for that early phase of treatment. By comparison, the cost-effectiveness of buprenorphine as a maintenance agent versus the current standard of methadone is slightly more in question, with some studies indicating that expanding methadone therapy would be the best alternative. Still, other studies, and especially those that considered the broadest societal costs and benefits (crime, travel time to clinics, access to care, etc.), demonstrate that either buprenorphine is dominant over methadone (overall cheaper and more effective), or at least that it is comparable with regards to its benefit-to-cost ratios. In summary, across all studies reviewed, it can be said that buprenorphine is either: almost as effective, equivalent to, or better than methadone—all conclusions that point toward expanded use.

[xi] As of February 2007.

Table 1. Summary of recent (1993 to 2006) empirical studies, or systematic reviews regarding methadone and buprenorphine treatment for heroin addiction. References are sorted in reverse chronological order. Treatment phases considered are: maintenance (i.e., long-term after detoxification) and detoxification (short-term, acute therapy initiation). Study design types are three-fold: 1) literature review, 2) clinical trial, or 3) modeling (based on secondary source data). A "favorable" appraisal of buprenorphine means that the study concluded that the buprenorphine therapy represents a reasonable, if not dominant, alternative as a treatment for heroin addiction. All 12 studies that looked at buprenorphine found that it was a favorable treatment option.

First Author (Year) ***Journal*** [ref]	**Appraisal of Buprenorphine**	**Treatment Phase (Drugs)** ***Study Design***	**Description/Method**	**Main Results**
Mattick (2006) *Cochrane Dbase of Systematic Reviews* [33]	Favorable, but methadone superior	Maintenance (buprenorphine, methadone, and placebo) *Literature review—meta-analysis*	13 studies, n=2,544, 12 double-blind. Individual study sample sizes ranged from 51-736. Most studies looked at treatment retention and urinalysis as outcome indicators, only one reported crime data.	Relative efficacy: Methadone>buprenorphine>placebo. (e.g., flexible dosing regimen trials revealed that methadone is 18 percent more likely to yield increased treatment retention).
Shanahan (2006a) *Australian NZ. J Pub Hlth* [32]	Favorable	Maintenance (methadone or buprenorphine) *Trial—pre/post*	Australian trial. n=745, 80 percent completed 12 months, >50 percent with psychopathology, not controlled or randomized.	First 12 month treatment costs were ~4,236 USD. Buprenorphine or methadone treatment of 12 months correlated with: 15.3 more heroin free days in month 12, and 53 percent crime reduction.
Shanahan (2006b) *Addictive Behavior* [31]	Favorable	Detoxification, (anesthesia, buprenorphine, clonidine) *Trial—randomized*	Reviewed 5 different methods of detoxification (first 7 days of treatment), including buprenorphine, anesthesia or sedation, and clonidine therapies (or other medicines to address symptoms) both inpatient and	Outpatient buprenorphine therapy was the most cost-effective therapy with regard to both outcomes. For example, 65% of the buprenorphine sample entered post-detox treatment programs in conjunction with mean treatment

			outpatient. Outcomes assessed were heroin abstinence and entry to post-detoxification programs. Pooled 7 separate trials. Sensitivity analysis varying input costs yielded no change in conclusions.	costs of ~320 USD, whereas the analogous rates for detox under sedation cost nearly 1,300 USD.
Simoens (2006) *Drug and Alcohol Depend* [30]	Favorable	Maintenance (buprenorphine and methadone) *Literature review*	Comprehensive review of cost-effectiveness (CE) and cost-benefit (CB) literature from 1995 to 2005. 105 econometric, medical, and psychological articles reduced to 7 CE and 5 CB studies for review. Discussion notes that implementation issues, including potential for abuse of therapeutic agents, are of concern.	-Incremental cost-effectiveness ratios for community opioid maintenance generally ranged from 3,451 USD to 9,103 USD per quality adjusted life year (QALY), in 1996 dollars. -Both US and UK studies reported benefit-cost ratios favoring methadone treatment ranging from 3:1 to 15:1. -Moderate as opposed to high levels of medical and psychosocial support services appeared to be most CE. -Efficacy of buprenorphine and methadone was comparable. -Only four of 12 studies provided full societal perspective (e.g., crime reduction).
Amato (2005) *Journal of Substance Abuse Treatment* [5]	Favorable	Maintenance (buprenorphine and methadone) *Literature review*	Cochrane-style review of 52 single studies including >12,000 subjects. 10 were controlled prospective studies. Methadone (varying doses), buprenorphine (varying doses), heroin, and LAAM maintenance studies were reviewed. Outcomes included: treatment retention, illicit heroin use, and mortality and crime rates.	<u>Retention rates:</u> 1 study, n=165: Methadone vs. no treatment (51% vs. 21%, $p<0.05$). 5 studies, n=449: Methadone (high dose) vs. buprenorphine (high dose) (52% vs. 41%, $p>0.05$, not significant, but trend favoring methadone). 5 studies, n=1,316: Buprenorphine (various doses) vs. placebo (61-55% vs. 41-38%, $p<0.05$).

				Crime activity across 3 studies was 3% in methadone group and 12% in untreated groups (p>0.05, not significant).
Harris (2005) *Pharmacoeconomics* [29]	Favorable	Maintenance (methadone vs. buprenorphine) *Trial—randomized*	Australian trial. n=139. Social costs included: health, crime, and transport to care. Benefits were heroin free days and (quality adjusted life years) QALYs. <4% of population reported any crime. Randomized, open-label. Urine tests confirmed self-report of heroin free days >75% of the time. 12 month trial, drop out rate=50 percent.	Intent to treat analysis: after 12 months heroin free days were 225 and 222 for methadone and buprenorphine, respectively (not significant); month 12 involved 21.6 and 23.6 heroin free days, far higher than the month prior to treatment (11.4 and 9.9 heroin free days) (p<0.05). Month 12 QALYs favored buprenorphine over methadone at 0.63 vs. 0.58 (no illness = 1.0) (not significant). Per added QALY, methadone was less expensive by ~26,000 USD when compared directly to buprenorphine.
Gowing (2004) *Cochrane Dbase of Systematic Reviews* [28]	Favorable	Detoxification (buprenorphine vs. methadone or clonidine) *Literature review*	Buprenorphine as a therapy for acute withdrawal symptoms is reviewed (treatment days 0-20). Outcomes: intensity, duration, and adverse effects of withdrawal (e.g., pain, chills, nausea, etc.). 14 randomized control and four non-randomized control studies were reviewed. Treatment settings were principally inpatient (11 studies). Comparison drugs were clonidine and methadone.	Vast majority of studies favored buprenorphine, especially over the effects of clonidine.

Doran (2003) *Drug and Alcohol Depend* [26]	Favorable, but methadone slightly superior	Maintenance (buprenorphine vs. methadone) *Trial—randomized*	From 1996-98 405 adults across 3 clinics were randomized to buprenorphine or methadone. Valuation of resources included: -Direct and indirect staff time -Meds and their dispensing -Supplies 277 subjects lost to follow-up.	Six months post-treatment increases in number of heroin free days Methadone=6.84±10.9 days/month Buprenorphine=5.27±9.96 days/month (not significant) <u>Six month treatment costs per enrollee</u> Methadone ~920 USD Buprenorphine ~1122 USD
Healy (2003) *Journal of Health Services Research Policy* [25]	None	Maintenance (methadone) *Trial—pre/post*	Cost-effectiveness between treatment costs and crime counts. Treatments evaluated: methadone in community, inpatient, or residential rehabilitation. Binary covariate: injection drugs users or not. 54 site study of >1,000 "problem" heroin users in the UK. Participants self-select therapy. Recruitment in 1995, one year follow-up data reviewed on 62% of sample (other data said to "not be usable"). Multivariate approach to estimating costs per each (self-reported) crime prevented.	<u>Crime count before (3 month prevalence)</u> Mean = 49.9 Median = 2 <u>Crime count after (3 month prevalence)</u> Mean = 13.1 Median = 0.0 Cost estimates per crime prevented by methadone treatment ~192 USD, with outliers removed ~322 USD. Crime type ranged from burglary to shoplifting and prostitution. Injectors were worse off than non-injectors.
Lavignasse (2002) *Ann Med Interne* [6]	Favorable	Maintenance (buprenorphine) *Trial—pre/post*	Selection of adult subjects made by 300+ French physicians. Baseline and six month interviews. 81 percent male, 57 percent had personal residence, 35 percent history of jail. Response and 6 month retention rates	<u>Change from baseline to six months</u> Unemployment: 11.7% to 10.4% (not significant) Heroin use: 75% to 14% (p<0.0001) Injectors: 65% to 35% (p<0.0001) Abscesses: 5.6% to 3.9% (not significant)

			>72 percent (original sample size=690).	Arrests: 20% to 9% (p<0.0001) Court appearances: 14% to 7% (p<0.0001) Sensation of being a threat to your partner: 57% to 17% (p<0.0001)
Barnett (2001) *Addiction* [10]	Favorable, but methadone superior	Maintenance (buprenorphine vs. methadone) *Modeling—cost-effectiveness*	Calculation of cost-effectiveness of expanding opiate maintenance therapy with buprenorphine. Variable input parameters: -Hi (40%) and Low (10%) HIV prevalence -Shared injection rates -Annual number of sex partners -Annual mortality from non-HIV causes -Annual graduation rate from therapy -Various buprenorphine prices ranging from 5 to 30 USD per dose.	Expansion of methadone treatment was always the most cost-effective approach. Most scenarios of methadone and buprenorphine had cost-effectiveness ratios lower than 50,000 USD per additional QALY indicating that they are worthy of adoption. Exceptions were buprenorphine scenarios where drug costs were projected to be very high (30 USD per dose) and where half of all buprenorphine users were enticed away from methadone therapy—i.e., direct substitution rather than treatment population expansion.
Rosenheck (2001) *Drug and Alcohol Depend* [11]	Favorable	Maintenance (buprenorphine vs. methadone) *Modeling—cost-effectiveness*	Cost estimates associated with office-based buprenorphine therapy were determined. Assumes weekly administration and that counseling fees would be reduced with buprenorphine. Varied costs: -Medication (buprenorphine at 4-8 USD per 12 mgs) -Dispensing	<u>Year 1</u> *Low cost estimates* Buprenorphine= 2,869 USD Methadone= 3,119 USD *High cost estimates* Buprenorphine= 6,170 USD Methadone= 5,417 USD <u>Subsequent years</u> *Low cost estimates* Buprenorphine= 2,261 USD Methadone= 2,779 USD

			-Counseling -Facilities -Toxicology screenings	*High cost estimates* Buprenorphine= 4,843 USD Methadone= 5,001 USD
Kosten (1993) *The Journal of Nervous and Mental Disease* [20]	Favorable, but methadone superior	Maintenance, (buprenorphine vs. methadone) *Trial—randomized*	140 subjects followed in New Haven, CT. Buprenorphine at two doses (2mg and 6mg) compared to methadone (35-65mg). Double-dummy placebo design (each participant got two doses one real, the other placebo)—randomization to one of the four dose/drug defined groups. Six month trial included early counseling, random weekly urine tests. Outcomes: clinician completed index, self-report on drug use and urine screening.	Methadone was superior overall. Authors speculate that higher doses of buprenorphine may be useful. <u>Intent-to-treat analysis (n=140)</u> *Mean retention (methadone low and high vs. buprenorphine low and high)* 18 and 20 weeks vs. 12 and 14 weeks ($p<0.0005$) For 73 completers, methadone was superior, e.g., expenditures on heroin/month: Methadone 35mg= 50 USD Methadone 65mg= 90 USD Buprenorphine 2mg= 260 USD ($p<0.05$) Buprenorphine 6mg= 95 USD

References

1. Moynihan, D.P. *One hundred years of heroin*, in *One hundred years of heroin*, D.F. Musto, Editor. 2002, Aurburn House: Westport, CT. p. 23-38.

2. Crum, R.M. *Chapter 3: Epidemiology of opioid use, abuse, and dependence*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 43-55.

3. Stoller, K.B. and G.E. Bigelow. *Chapter 1: Introduction and historical overview*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 3-17.

4. Sung, S. and J.M. Conry. *Role of buprenorphine in the management of heroin addiction.* Ann Pharmacother, 2006. **40**(3): p. 501-5.

5. Amato, L., et al. *An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research.* J Subst Abuse Treat, 2005. **28**(4): p. 321-9.

6. Lavignasse, P., et al. *Economic and social effects of high-dose buprenorphine substitution therapy. Six-month results.* Ann Med Interne (Paris), 2002. **153**(3 Suppl): p. 1S20-6.

7. Lewis, D.C. *Access to narcotic addiction treatment and medical care: prospects for the expansion of methadone maintenance treatment.* J Addict Dis, 1999. **18**(2): p. 5-21.

8. Mark, T., et al. *The economic costs of heroin addiction in the United States.* Drug and Alcohol Dependence, 2001. **61**(2): p. 195-206.

9. McCarty, D., R.G. Frank, and G.C. Denmead. *Methadone maintenance and state Medicaid managed care programs.* Milbank Q, 1999. **77**(3): p. 341-62, 274.

10. Barnett, P.G., G.S. Zaric, and M.L. Brandeau. *The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States.* Addiction, 2001. **96**(9): p. 1267-78.

11. Rosenheck, R. and T. Kosten. *Buprenorphine for opiate addiction: potential economic impact.* Drug Alcohol Depend, 2001. **63**(3): p. 253-62.

12. Stoller, K.B. and G.E. Bigelow. *Chapter 2: Regulatory, cost, and policy issues*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 18-42.

13. Clarke, H. and U. La Trobe. *Economic analysis of public policies for controlling heroin use.* Australian Economic Papers, 2003. **42**(2): p. 234.

14. Walsh, S.L. and E.C. Strain. *Chapter 4: Pharmacology of methadone*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 59-76.

15. Kleber, H.D. *Methadone: The drug, the treatment, the controversy*, in *One hundred years of heroin*, D.F. Musto, Editor. 2002, Aurburn House: Westport, CT. p. 149-158.

16. Saxon, A.J. and D. McCarty. *Challenges in the adoption of new pharmacotherapeutics for addiction to alcohol and other drugs.* Pharmacol Ther, 2005. **108**(1): p. 119-28.

17. Strain, E.C. *Chapter 10: Pharmacology of buprenorphine*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 213-229.

18. Fiellin, D. and E.C. Strain. *Chapter 12: Office-based treatment with buprenorphine and other medications*, in *The treatment of opioid dependence*, E.C. Strain and M.L. Stitzer, Editors. 2006, Johns Hopkins University Press: Baltimore. p. 253-276.

19. Boardman, A.E. *Cost-benefit analysis: concepts and practice*. 3rd ed. 2006, Upper Saddle River, N.J.: Pearson/Prentice Hall. xv, 560.

20. Kosten, T.R., et al. *Buprenorphine versus methadone maintenance for opioid dependence.* J Nerv Ment Dis, 1993. **181**(6): p. 358-64.

21. Amato, L., et al. *Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification.* Cochrane Database Syst Rev, 2004(4): p. CD005031.

22. French, M.T. *Cost-effectiveness of buprenorphine maintenance versus methadone maintenance.* Addiction, 2001. **96**(10): p. 1515-7.

23. Reuter, P. *Cost-effectiveness estimates for buprenorphine should factor in crime.* Addiction, 2001. **96**(10): p. 1515.

24. Sindelar, J.L. *Opioid maintenance: the politics matter.* Addiction, 2001. **96**(10): p. 1517-8.

25. Healey, A., et al. *Criminal outcomes and costs of treatment services for injecting and non-injecting heroin users: evidence from a national prospective cohort survey.* J Health Serv Res Policy, 2003. **8**(3): p. 134-41.

26. Doran, C.M., et al. *Buprenorphine versus methadone maintenance: a cost-effectiveness analysis.* Drug Alcohol Depend, 2003. **71**(3): p. 295-302.

27. Caplehorn, J. and J.J. Deeks. *A critical appraisal of the Australian comparative trial of methadone and buprenorphine maintenance.* Drug Alcohol Rev, 2006. **25**(2): p. 157-60.

28. Gowing, L., R. Ali, and J. White. *Buprenorphine for the management of opioid withdrawal.* Cochrane Database Syst Rev, 2004(4): p. CD002025.

29. Harris, A.H., E. Gospodarevskaya, and A.J. Ritter. *A randomized trial of the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting.* Pharmacoeconomics, 2005. **23**(1): p. 77-91.

30. Simoens, S., et al. *Pharmaco-economics of community maintenance for opiate dependence: A review of evidence and methodology.* Drug Alcohol Depend, 2006.

31. Shanahan, M.D., et al. *A cost-effectiveness analysis of heroin detoxification methods in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD).* Addict Behav, 2006. **31**(3): p. 371-87.

32. Shanahan, M., et al. *Patterns and costs of treatment for heroin dependence over 12 months: findings from the Australian Treatment Outcome Study.* Australian & New Zealand Journal of Public Health, 2006. **30**(4): p. 305.

33. Mattick, R.P., et al. *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database Syst Rev, 2006(3): p. CD002207.