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RESEARCH REPORT

A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence

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Abstract

Background. *The unique pharmacological properties of buprenorphine may make it a useful maintenance therapy for opiate addiction. This meta-analysis considers the effectiveness of buprenorphine relative to methadone.* **Methods.** *A systematic literature search identified five randomized clinical trials comparing buprenorphine to methadone. Data from these trials were obtained. Retention in treatment was analyzed with a Cox proportional hazards regression. Urinalyses for opiates were studied with analysis of variance and a common method of handling missing values. A meta-analysis was used to combine these results.* **Results.** *Subjects who received 8–12 mg/day buprenorphine had 1.26 times the relative risk of discontinuing treatment (95% confidence interval 1.01–1.57) and 8.3% more positive urinalyses (95% confidence interval 2.7–14%) than subjects receiving 50–80 mg/day methadone. Buprenophrine was more effective than 20–35 mg/day methadone. There was substantial variation in outcomes in the different trials.* **Conclusions.** *The variation between trials may be due to differences in dose levels, patient exclusion criteria and provision of psychosocial treatment. The difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the differences are small compared to the wide variance in outcomes achieved in different methadone treatment programs. Further research is needed to determine if buprenorphine treatment is more effective than methadone in particular settings or in particular subgroups of patients.*

Introduction

There are some 750 000 heroin users in the United States.[1] While some individuals with opiate dependence disorders are successfully treated with naltrexone or in exclusively psychosocial treatment programs, methadone maintenance is the only widespread treatment that has high rates of success in reducing intravenous use of heroin. Despite the demonstrated efficacy of methadone, there were only 179 000 patients enrolled in US methadone treatment programs in 1998.[2]

A number of factors have limited the use and effectiveness of this treatment. Federal, state and local laws limit use; new methadone clinics have

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difficulty obtaining approval from local authorities.[3] Many treatment programs dispense methadone at doses which have been found to be inadequate.[4,5] Some patients wish to avoid the social stigma associated with methadone. Others do not like the subjective effects of methadone or the structure of treatment, including daily clinic visits and periodic psychosocial interventions. Public funding is inadequate to provide treatment to all who desire it.

Buprenorphine has been proposed as a new therapy that could help those who are not already receiving treatment, stem the incidence of HIV and other diseases and help alleviate other problems resulting from opiate abuse. It has several potential advantages. Since it is a partial agonist, there is a ceiling on its ability to cause respiratory depression; administration of buprenorphine is thus less likely to result in an overdose. Its use results in less physical dependence, so that it is easier to detoxify from buprenorphine than from methadone.[6]

A combination of buprenorphine and the opiate antagonist naloxone is being considered as a take-home maintenance therapy. If the combination drug is administered by injection by an opiate dependent individual, the naloxone precipitates acute abstinence. This property limits the possibility of abuse. A trial of the safety and effectiveness of this combination drug has been completed. A new trial will consider the use of the combination drug as a maintenance therapy prescribed in primary care practice.

Health-care payers will add buprenorphine to their formularies only if its benefits justify its cost. Unfortunately, there is no information about the long-term cost or effectiveness of buprenorphine to assist payers in making this decision. There is, however, a great deal of information about the long-term effects of methadone therapy. Knowledge of the relative effectiveness of buprenorphine and methadone could be combined with this information to model buprenorphine cost-effectiveness. Several clinical trials have compared the efficacy of buprenorphine and methadone for periods of 6 months or less. These short-term trials represent the only available information to estimate the effectiveness of buprenorphine over the long-term in actual clinical practice. This paper presents a meta-analysis of five trials that compared buprenorphine to methadone.

Methods and data

We used Medline to identify all peer-reviewed reports of double-blind randomized clinical trials that compared methadone to buprenorphine as an opioid substitution therapy published in the English language before 1998. We found five published studies which tested buprenorphine in daily doses of at least 6 mg.[7–11] We found a sixth trial that tested a lower, 2-mg dose of buprenorphine.[12] We did not include it in our study because this dose was too low to be comparable to the data from the other trials.

In each study, subjects were randomly assigned to receive either methadone or buprenorphine. The characteristics of the five studies are presented in Table 1. Buprenorphine doses varied between 6 mg and 12 mg per day. Methadone doses varied from 50 to 80 mg per day. Four of the studies included additional groups that received a lower dose of methadone; two studies included additional groups receiving a lower dose of buprenorphine. Our primary analysis compared the groups receiving the largest dose of each drug. Adoption of a candidate pharmaceutical depends on its comparison to the incumbent drug at the recommended dose; guidelines for methadone substitution therapy recommend a dose of at least 60 mg, and note that higher doses are often required.[13] There are not yet any guidelines for buprenorphine therapy. The trials we studied considered doses of 6–12 mg/day; the higher doses were employed in the more recent study. Whether the buprenorphine doses used in these studies represents the appropriate dose for comparison is an issue we consider in the Discussion.

The studies followed patients for periods of 16–26 weeks. Two of the studies also followed patients during a subsequent 8–10-week-long detoxification period but we did not consider these detoxification periods in our analysis.

Although a variety of outcomes were measured in these five trials, two measures were used in all studies. Every study conducted a periodic urinalysis for opiates and reported the length of time that each subject remained in treatment.

The goal of maintenance therapy is to reduce opiate use. This can be regarded as having three dimensions: the reduction in use that occurs while therapy is received, the length of time that therapy continues, and the effect of the therapy after it is discontinued. The urinalysis results represent a measure of this first dimension. Re-

Table 1. *Randomized clinical trials comparing buprenorphine to methadone for opiate dependence*

Study	Methadone dose (mg/day)	Buprenorphine dose (mg/day)	Study length (weeks)	Number of subjects[a]
Johnson (1992)	60	8	17[b]	107
Strain (1994)	50	8	16[c]	164
Schottenfeld (1997)	65	12	24	57
Ling (1996)	80	8	26	150
Kosten (1993)	65	6	24	62

[a] Subjects in these two treatment groups receiving the doses listed. [b] Followed by 8-week detoxification period. [c] Followed by 10-week detoxification period.

tention data is a measure of the second. Since no data were gathered on individuals who discontinued therapy, the third dimension was not measured. This benefit is likely to be negligible, however. Other studies have found that most individuals who drop out during their first year of methadone maintenance return to opiate abuse.[14]

In order to apply the same analytical methods to all data, we obtained the original urinalysis and retention data on the subjects in each of the individual studies. All studies regularly screened subjects' urine for illicit opiates for as long as the subject continued in the study. The testing schedule varied from a minimum of one test per week to a maximum of three.

Each subject had an outcome, which was the number of events (positive urinalyses) divided by the number of possible events (number of urinalyses). The urinalysis data of each subject were characterized by a number between zero and one. The mean of these values was determined for each group, and the difference in group means was found for each study. The meta-analysis estimated the average size of this difference. This was the mean difference between buprenorphine and methadone treatment groups while participants were still in treatment.

We used two different methods of handling missing urinalyses. The first method treated missing tests as positive, thereby creating a complete dataset. This assumes that a subject who missed providing a specimen had been using illicit opiates. Since we considered only the period while the subject was retained in treatment, the assumption was not applied to tests missed because subjects had dropped out or had been terminated from the study. The second method ignored missing values. This approach is valid if the missing status of the specimen provides no information—if subjects who had used illicit opiates were just as likely to fail to provide a urine specimen as those who had abstained.

The other outcome measure was the length of time the subject was retained in treatment. Since patients were followed only until the last day of each study, this outcome was censored by the length of follow-up. We analyzed data from each study with a Cox proportional hazards model. The regression used the number of days the subject was retained as the dependent variable, and a single independent variable, an indicator which took a value of 1 if the subject was in the buprenorphine treatment group. To provide a clear interpretation of the effect, we expressed the hazard parameter as the relative risk of discontinuing buprenorphine treatment compared to methadone.

A detailed description of the statistical methods is available from the authors upon request. For each study, we determined the difference in outcomes between the treatment groups. For the urinalysis data, we calculated the difference between the means of the buprenorphine and methadone treatment groups. For the retention data, we used the coefficient from the Cox proportional hazards regression. We pooled the standard deviations of each treatment group to find the variance of the urinalysis data. We took the square of the standard error of the Cox regression parameter to find the variance of the retention data. We found the mean treatment effect, weighting studies by the reciprocal of the variance. The statistical significance of differences was estimated using variance estimated with the appropriate meta-analysis method. We used the homogeneity test to evaluate the validity of the statistical assumptions needed to pool data for meta-analysis.

Table 2. *Subjects' mean percentage positive urinalysis for illicit opiates in randomized clinical trials comparing buprenorphine to methadone for opiate dependence*

Study	Buprenorphine	Methadone	Difference	Confidence interval	Homogeneity test (p value)
Johnson (1992)	0.588	0.610	−0.022	−0.142–0.097	
Strain (1994)	0.547	0.497	0.051	−0.044–0.146	
Schottenfeld (1997)	0.544	0.389	0.155*	0.001–0.310	
Ling (1996)	0.542	0.372	0.169*	0.066–0.273	
Kosten (1993)	0.781	0.537	0.244*	0.085–0.404	
Summary based on five studies				(fails homogeneity test)	0.034*
Summary based on four studies (excluding Kosten)			0.083*	0.027–0.140	0.074

*$p < 0.05$.

Results

The differences in the urinalysis results of the methadone and buprenorphine groups are presented in Table 2. This analysis treated missing values as if they were positive. The homogeneity test found that the effect of these five studies could not be considered homogeneous ($\chi^2 = 10.4$, df = 4, $p = 0.033$), so it was not appropriate to report the mean difference in the effect based on all five studies. When we limited the analysis to the four studies that used at least 8 mg of buprenorphine, the homogeneity test was no longer significant (this excluded the trial reported by Kosten, which used a 6-mg dose). In these four studies subjects receiving buprenorphine had an average of 8.3% more positive urinalyses than subjects receiving methadone ($Z = 2.91$, $p = 0.002$). The 95% confidence interval was 2.7–14%.

Adopting the assumption that missing values could be ignored had little effect on the result. Subjects receiving buprenorphine had 8.0% more positive tests ($Z = 2.62$, $p = 0.004$). The 95% confidence interval was 2.0–13.9%.

The effect of treatment on subject retention is presented in Table 3. Using all five studies, the test of homogeneity is not significant at the .05 level ($\chi^2 = 8.1$, df = 4, $p = 0.088$). We calculated the mean difference in retention by combining the Cox-regression parameters. Subjects receiving buprenorphine had an average of 1.26 times the relative risk of discontinuing treatment per unit of time than subjects receiving methadone. The difference in risk was significant ($Z = 2.07$, $p = 0.019$), with a 95% confidence interval of 1.01–1.57.

When the retention analysis was limited to the four studies that tested 8 mg or more of buprenorphine, the subjects receiving buprenorphine had 1.17 times the risk of discontinuing treatment. This value was not significantly different from one ($Z = 1.36$, $p = 0.087$), with the 95% confidence interval ranging from 0.93 to 1.48.

The two outcome measures used by these trials are highly correlated. Table 4 presents a ranking of studies according to each outcome. Each study was ranked by the retention outcome, in the order of the lowest to highest relative hazard ratio between buprenorphine and methadone. The trial reported by Johnson is at the top of the ranking as it was the study in which buprenorphine was the most effective at retaining patients. The trial reported by Kosten is at the bottom of the ranking because it showed buprenorphine to be the least effective.

Table 4 also presents the ranking of studies by urinalyses results. The trial reported by Johnson is again at the top of the ranking, as the urinalysis results in this study showed buprenorphine to be the most effective compared to methadone. The study reported by Kosten is again at the bottom of the ranking; the urinalysis data showed buprenorphine to be the least effective compared to methadone. The ranking of the five studies in terms of the relative effectiveness of buprenorphine is exactly the same for both outcomes.

The studies employed different doses of both drugs. In order to combine these into a simple, one-dimensional measure, we divided the buprenorphine dose by the methadone dose and ranked the studies by this measure (see Table 4). There was some correlation between the dose

Table 3. *Difference in retention in treatment in randomized clinical trials comparing buprenorphine to methadone for opiate dependence*

Study	Relative hazard ratio	Confidence interval	Homogeneity test (p value)
Johnson (1992)	0.830	0.515–1.339	
Strain (1994)	1.048	0.679–1.617	
Schottenfeld (1997)	1.343	0.610–2.960	
Ling (1996)	1.534*	1.057–2.226	
Kosten (1993)	2.437*	1.208–4.917	
Summary based on five studies	1.263*	1.013–1.575	0.088
Summary based on four studies (excluding Kosten)	1.175	0.931–1.483	0.224

*$p < 0.05$.

used and the outcomes in the study. The study with the lowest relative buprenorphine dose, the trial reported by Kosten, also found buprenorphine to have the lowest relative effectiveness. Ling's study used the next lowest relative dose and reported the second worst result. The starting doses employed in Strain's study were second in both the dose and outcomes rankings.

In the other two trials the relationship between dose and outcomes was not clear. The Schottenfeld study employed the highest relative dose of buprenorphine but ranked third in its findings of the relative effectiveness of buprenorphine. The Johnson study used the third highest relative dose of buprenorphine and found the greatest relative effectiveness of buprenorphine.

We considered how the meta-analysis was affected by the dose of methadone used in the comparison group. We considered the three studies that tested at least 8 mg/day of buprenorphine, and included an additional low-dose (20–30 mg/day) methadone treatment group.[7,8,10] When compared to low-dose methadone, subjects receiving buprenophine had significantly fewer positive urinalyses. The buprenorphine group had 8.4% fewer positive urinalyses (95% confidence interval 1.2–15.6% fewer) than the low-dose methadone group. This analysis assumed missing tests were positive; if missing tests are ignored, the buprenorphine group had 10.2% fewer positive tests (a difference that was also significant, with confidence interval of 2.4–18.0%).

The buprenorphine group also had a lower, but non-significant, risk of discontinuing treatment than subjects receiving low-dose methadone. Buprenorphine subjects had 0.86 times the relative risk of discontinuing treatment (95% confidence interval of 0.66–1.22).

Discussion

This meta-analysis determined that subjects receiving a daily dose of between 8 and 12 mg of buprenorphine were 1.26 times more likely to drop out of treatment than subjects receiving 50–80 mg/day of methadone, and that they were 8.3% more likely to have a positive

Table 4. *Ranking of effect size and relative treatment dose in randomized clinical trials comparing buprenorphine to methadone for opiate dependence*

Study	Rank of effect of buprenorphine relative to methadone		Buprenorphine dose divided by methadone dose	Rank of relative dose of buprenorphine compared to methadone
	Retention	Urinalyses		
Johnson (1992)	1	1	0.13	3
Strain (1994)	2	2	0.16	2
Schottenfeld (1997)	3	3	0.18	1
Ling (1996)	4	4	0.10	4
Kosten (1993)	5	5	0.09	5

urinalysis for opiates. The finding is consistent with preliminary data from a European trial, where buprenorphine was associated with lower retention and more positive urinalyses.[15]

The pharmacological properties of buprenorphine suggest that it should be safer and result in less physical dependence than methadone. These considerations may be critical to the decision about whether buprenorphine should be adopted. Unfortunately, data about these effects were not gathered in a way that allows meta-analytical comparison, and we were unable to identify this potential advantage of buprenorphine therapy.

Although we found a statistically significant difference in the effectiveness of buprenorphine and methadone, these differences do not appear to be of very great clinical significance. Much larger differences in the dropout rates have been observed with different doses of methadone. For example, patients who received doses of less than 60 mg of methadone had nearly five times the risk of dropping out as those who received doses of 80 mg or more.[16] Patients who were not informed of their methadone dose were 3.17 times more likely to drop out than patients who were informed of their dose.[17]

A US federal audit found that 21 of 24 methadone programs used doses of less than 60 mg/day[4] while a survey of methadone programs found that 25% had policies against prescribing more than 60 mg/day.[18] The differences between optimal and current practice in many opiate substitution programs are associated with much greater effect on outcomes than the difference between buprenorphine and methadone.

The difference in effects observed in the different trials may be attributable to the dose used, and to other features of study design. These include the characteristics of patients, the amount of psychosocial services that were provided and other features of the study protocol.

In the three studies which found methadone to be significantly more effective than buprenorphine,[8–10] all three authors suggested that higher doses of buprenorphine may be needed. The most recent of these papers, which reported the results of the highest relative dose of buprenorphine, concluded with the comment that "daily doses even higher than 12 mg (of buprenorphine) … may be required to achieve optimal results".[8] On the other hand, as a partial agonist, at a higher dose buprenorphine limits its own effect; higher doses may limit or even reduce its effectiveness. Our analysis cannot tell which of these two views is correct. Additional studies will need to determine if buprenorphine doses of higher than 12 mg/day are more effective, or whether the partial agonist properties of buprenorphine limit its effectiveness.

We found that an 8–12-mg/day dose of buprenorphine was more effective than low dose methadone. We report the comparison to the higher dose of methadone as our primary result because we believe than an innovative therapy must be compared to best available standard therapy. The best standard therapy is represented by the high methadone dose groups. Indeed, the 50–80-mg/day methadone dose may actually be too low for many patients. Randomized trials have established that a daily methadone dose of between 80 and 100 mg is superior to 40–50 mg.[19,20] The successful treatment of some patients requires doses well in excess of 100 mg/day methadone.[21]

Aside from the differences in dose, these studies also enrolled different types of patients. The Schottenfeld study included only those patients who were dependent on cocaine as well as opiates. Subjects in the other studies reported lower levels of cocaine dependence; Ling's study excluded cocaine dependent subjects altogether. The study reported by Strain included only those patients with little prior experience in methadone maintenance. Three studies, those of Kosten, Ling and Schottenfeld, excluded subjects who were dependent on alcohol or sedatives. Buprenorphine performed the poorest in these three studies.

The trials also differed in the amount of counseling that was offered to participants. In the Johnson study counseling sessions were voluntary. At the other extreme, the Schottenfeld study required subjects to attend group therapy; treatment was discontinued if three consecutive sessions were missed.

There are several limits to the findings of this meta-analysis. It is possible that a modest change in buprenorphine dose may have resulted in substantially different outcomes. The trials were of inadequate size to consider safety issues, such as the danger of overdose. The trials may not adequately represent the clinical effectiveness of buprenorphine in actual clinical practice, where different types of patients may be treated with different psychosocial elements. Buprenorphine

may prove to be most effective in certain subgroups of patients.[22] Effectiveness may depend on other treatment factors. The study in which buprenorphine was the most successful involved little psychosocial intervention.[7] In addition, buprenorphine was dispensed as a liquid in the trials; in actual practice it will probably be dispensed as a tablet compounded with naloxone.

Methadone is not available to all opiate dependent individuals seeking treatment, and there are limited opportunities of expanding methadone treatment programs in the United States. This analysis of buprenorphine found it to be nearly as effective as methadone. Buprenorphine has the potential to reduce the harm caused by intravenous drug abuse. Health-care decision-makers will need to decide whether buprenorphine maintenance is worth adopting. They will need to consider the cost of this new maintenance therapy and its value in reducing the effects of opiate dependence, including HIV infection and high rates of mortality. Future trials will be needed to consider safety, the effect of dose, treatment setting, drug formulation and whether there are subgroups of patients who can best benefit from this treatment.

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References

1. SPENCER, B. D. (1989) On the accuracy of estimates of numbers of intravenous drug users, in: TURNER, C. F., MILLER, H. G. & MOSES, L. E. (Eds) *AIDS: sexual behavior and intravenous drug use*, pp. 429–446 (Washington, DC, National Academy Press).
2. AMERICAN METHADONE TREATMENT ASSOCIATION (1998) Methadone Maintenance Provider Survey (New York, NY, American Methadone Treatment Association).
3. COOPER, J. R. (1989) Methadone treatment and acquired immunodeficiency syndrome, *Journal of the American Medical Association*, 262, 1664–1668.
4. US GENERAL ACCOUNTING OFFICE (1990) Methadone maintenance: some treatment programs are not effective; greater federal oversight needed (Washington, DC, US General Accounting Office).
5. BALL, J. C. & ROSS, A. (1991) *The Effectiveness of Methadone Maintenance Treatment* (New York, Springer-Verlag).
6. JASINSKI, D. R., PEVNICK, J. S. & GRIFFITH, J. D. (1978) Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction, *Archives of General Psychiatry*, 35, 501–516.
7. JOHNSON, R. E., JAFFE, J. H. & FUDALA, P. J. (1992) A controlled trial of buprenorphine treatment for opioid dependence, *Journal of the American Medical Association*, 267, 2750–2755.
8. SCHOTTENFELD , R. S., PAKES, J. R., OLIVETO, A., ZIEDONIS, D. & KOSTEN, T. R. (1997) Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse, *Archives of General Psychiatry*, 54, 713–720.
9. KOSTEN, T. R., SCHOTTENFELD , R., ZIEDONIS, D. & FALCIONI, J. (1993) Buprenorphine versus methadone maintenance for opioid dependence, *Journal of Nervous and Mental Disease*, 181, 358–364.
10. LING, W., WESSON, D. R., CHARUVASTRA, C. & KLETT, J. (1996) A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence, *Archives of General Psychiatry*, 53, 401–407.
11. STRAIN, E. C., STITZER, M. L., LIEBSON, I. A. & BIGELOW, G. E. (1994) Comparison of buprenorphine and methadone in the treatment of opioid dependence, *American Journal of Psychiatry*, 151, 1025–1030.
12. BICKEL, W. K., STITZER, M. L., BIGELOW, G. E., LIEBSON, I. A., JASINSKI, D. R. & JOHNSON, R. E. (1988) A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts, *Clinical Pharmacology and Therapeutics*, 43, 72–78.
13. NIH CONSENSUS CONFERENCE (1998) Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, *Journal of the American Medical Association*, 280, 1936–1943.
14. BERTSCHY, G. (1995) Methadone maintenance treatment: an update, *European Archives of Psychiatry and Clinical Neuroscience*, 245, 114–124.
15. UEHLINGER, C., DEGLON, J., LIVOTI, S., PETITJEAN, S., WALDVOGEL, D. & LADEWIG, D. (1998) Comparison of buprenorphine and methadone in the treatment of opioid dependence. Swiss multicentre study, *European Addiction Research*, 4, 13–18.
16. CAPLEHORN, J. R. & BELL, J. (1991) Methadone dosage and retention of patients in maintenance

treatment, *Medical Journal of Australia*, 154, 195–199.

17. CONDELLI, W. S. & DUNTEMAN, G. H. (1993) Exposure to methadone programs and heroin use, *American Journal of Drug and Alcohol Abuse*, 19, 65–78.
18. D'AUNNO, T. & VAUGHN, T. E. (1992) Variations in methadone treatment practices. Results from a national study, *Journal of the American Medical Association*, 267, 253–258.
19. LING, W., CHARUVASTRA, C., KAIM, S. C. & KLETT, C. J. (1976) Methadyl acetate and methadone as maintenance treatments for heroin addicts. A veterans administration cooperative study, *Archives of General Psychiatry*, 33, 709–720.
20. STRAIN, E. C., BIGELOW, G. E., LIEBSON, I. A. & STITZER, M. L. (1999) Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial, *Journal of the American Medical Association*, 281, 1000–1005.
21. LEAVITT, S., SHINDERMAN, M., MAXWELL, S., EAP, C. & PARIS, P. (2000) When "enough" is not enough: new perspectives on optimal methadone maintenance dose, *Mount Sinai Journal of Medicine*, 67, 404–411.
22. RESNICK, R. B., RESNICK, E. & GALANTER, M. (1991) Buprenorphine responders: a diagnostic subgroup of heroin addicts? *Progress in Neuro-psychopharmacology and Biological Psychiatry*, 15, 531–538.