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Review

Clinical efficacy of buprenorphine: comparisons to methadone and placebo

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Abstract

Buprenorphine has been studied extensively since 1978 when it was initially proposed as an alternative to methadone for treatment of opioid dependence. Early work by Jasinski, Mello, Mendelson and their colleagues demonstrated buprenorphine's low physical abuse potential and its ability to substitute for heroin and reduce heroin self-administration in opiate-dependent humans. The subsequent early clinical studies suggested that, in clinical settings, buprenorphine was a safe and efficacious opiate dependence pharmacotherapy. Formal approval for general clinical use, however, required that systematic data be gathered on buprenorphine's safety and efficacy in larger groups and a series of controlled clinical trials was designed to evaluate its utility from a medication development perspective. In general, these trials adhered to one of three basic protocol designs: comparison of buprenorphine to methadone; dose comparisons using dose response as an indicator of efficacy; and comparison of buprenorphine to placebo. Retention in treatment, reduction in illicit drug use and craving, and patient and staff ratings of improvements were the most frequently used outcome indicators in these trials. Additional data collected included optimum dosing and dosage schedules, adverse reactions and common side-effects, and other information intended to clarify buprenorphine's benefit–risk relationship and to help prepare guidelines for its safe marketing and utilization by physicians in general clinical practice. This paper presents a review of the buprenorphine/methadone comparison trials conducted in the United States and two such trials conducted in Europe. Also reviewed are three placebo-controlled trials and a buprenorphine/methadone detoxification study. Overall, this series of studies did firmly establish the efficacy of buprenorphine alone and in comparison to methadone.

Keywords: Treatment; Pharmacotherapy; Buprenorphine

1. Introduction

This paper reviews studies conducted to evaluate the efficacy of buprenorphine for treatment of opiate dependence (Table 1). Because patients can readily identify the mood altering effects of opiate agonists, establishing the efficacy of a new opiate medication is often best accomplished by comparison with one of similar action and established effectiveness. Moreover, ethical consideration would dictate that new pharmacotherapeutic treatments be compared with "standard" or already proved treatments. Consequently, a series of controlled clinical trials was conducted to compare the safety and efficacy of buprenorphine to that of methadone in maintenance treatment and, where possible, the utility of buprenorphine in detoxification. In addition, some studies directly compared buprenorphine with placebo or with a placebo dose. Each of these types of studies are summarized below.

2. Buprenorphine versus methadone maintenance

2.1. Johnson et al. (1992)

2.1.1. Subjects and methods

This 25-week-study, conducted at the Addiction Research Center in Baltimore, MD, was the first published large controlled trial of buprenorphine in

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Table 1
Clinical trials assessing the efficacy of buprenorphine for the treatment of opiate dependence

Author/year	Methadone				Buprenorphine			
	Dose (mg)	*N*	Retention (%)	Urine	Dose (mg)	*N*	Retention (%)	Urine
Johnson et al., 1992	20	55	20	29% neg	8	53	42	53% neg
	60	54	32	44% neg				
Kosten et al., 1993	35	34	82	51% pos	2	28	54	27% pos
	65	35	63	52% pos	6	28	39	24% pos
Ling et al., 1996	30	75	45	68% neg	8	75	47	68% neg
	80	75	68	79% neg				
Schottenfeld et al., 1997	20	30	58	68% pos	4	29	48	74% pos
	65	28	72	40% pos	12	29	65	57% pos
Strain et al., 1994a,b	54 (50–90)	80	56	47% pos	8.9	84	56	55% pos
Uehlinger et al., 1998	69.8 (60–120)	31	90	59% pos	10.5 (8–16)	27	56	62% pos
Johnson et al., 1995		PLACEBO			2	60	62	76% pos
		60	28	96% pos	8	30	51	74% pos
					1	185	40	6% neg
Ling et al., 1998					4	182	51	10% neg
					8	188	52	10% neg
					16	181	61	14% neg

Buprenorphine comparisons to methadone and to placebo (or low dose placebo) are both shown.

the US and was considered by the food and drug administration (FDA) to be pivotal for filing of a new drug application (NDA). Prior to starting the study, the investigators had speculated that buprenorphine would have such clinical advantages over methadone as enhanced safety in overdose, longer duration of action, and a limited withdrawal syndrome. Utilizing a double-blind, double-dummy, parallel group design, 162 medically healthy, treatment-seeking opiate abusers between 21 and 50 years of age were randomly assigned in equal numbers to one of three treatment groups: 8-mg/day sublingual liquid buprenorphine, 20-mg/day oral methadone, or 60-mg/day oral methadone. Treatment induction varied from 3 to 9 days with the total induction and maintenance phase lasting 119 days, followed by 7 weeks of gradual dose reduction and 11 days of placebo. Relapse prevention counseling was offered, but not required. Groups were stratified for age, gender, and naloxone challenge withdrawal scores. Primary measures of efficacy were time in treatment (retention) and maintenance of abstinence as assessed by three-times-a-week urine specimens.

2.1.2. Results

Fifty subjects completed the 17-week-maintenance phase and, of these, 24 completed the entire 25-week-study. The most common reason for early termination was "no show", i.e. missed three consecutive medication visits (66%), followed by various reasons unrelated to the study (17%). Only four subjects (3%) terminated due to "adverse effects". At the end of 17 weeks, 42% of the buprenorphine group remained in treatment compared with 20% of the 20-mg/day methadone group ($P < 0.04$), and 32% of the 60-mg/day methadone group (not considered statistically significant). The percentage of opiate negative urines showed a similar trend. Considering missed samples as opiate positive, 53% of the urine samples contributed by the buprenorphine group during their tenure in the study were negative for opiates compared with 44 and 29%, respectively, for the high and low dose methadone groups. Although subjects in the 60-mg methadone group reported "liking" the treatment significantly more often than did the other two groups and reported a higher degree of euphoria, subjects on the high methadone dose also felt significantly more "hooked". Withdrawal scores were similar for all groups, possibly due to illicit "topping-off" with street opiates. Adverse events between groups were similar and consistent with opiate withdrawal.

2.1.3. Conclusion

The investigators concluded that 8-mg/day buprenorphine was clearly more effective than 20-mg/day methadone and comparable to 60-mg/day methadone in the treatment of opiate-dependent patients.

2.2. Kosten et al. (1993)

2.2.1. Subjects and methods

This 24-week, double blind, randomized trial compared 2- and 6-mg/day sublingual liquid buprenorphine with 35- and 65-mg/day methadone in 140 subjects meeting DSM-III criteria for opiate dependence. The investigators hypothesized that 6-mg/day buprenorphine would be more effective than 2-mg/day buprenorphine at keeping subjects in treatment and reducing illicit opiate use. Based on the Johnson et al. (1992) trial, the investigators also hypothesized that 6-mg/day bupre-

norphine would be equal to 35- or 65-mg/day methadone. Primary outcome measures for the study were treatment retention and use of illicit opiates as assessed by once weekly, randomized urinalysis and self-report. Other measures included weekly assessment of opiate withdrawal symptoms and a clinician completed addiction severity index (ASI) at intake.

2.2.2. Findings

Six-mg/day buprenorphine reduced illicit opiate use more effectively than 2-mg/day buprenorphine, but the higher dose was not associated with more patients retained in treatment. Although there was a substantial decline in self-reported opiate use in all groups, by the third month significantly more heroin abuse was reported in the 2-mg/day buprenorphine group than in the 6-mg/day buprenorphine group or either of the methadone groups. The relative low efficacy of 2-mg/day buprenorphine continued through month 6 of the trial. The increased abuse of opiates was also associated with persistent and significantly greater withdrawal symptoms. Treatment retention was significantly better on methadone (20 vs. 16 weeks) and more opiate-free urines were associated with the methadone subjects (51 vs. 26%). More patients on methadone achieved abstinence for at least 3 consecutive weeks.

2.2.3. Conclusion

As hypothesized, the higher dose of buprenorphine was more effective at reducing illicit opiate use than the lower dose, but in this study it was not better at retaining patients in treatment. Contrary to the investigator's expectations, 6-mg/day buprenorphine was not found to be equally effective to either 35- or 65-mg/day methadone. The investigators concluded that buprenorphine would be more favorably compared with methadone if the dosage were increased and that future comparison studies should expand the dosage of sublingual buprenorphine to a maximum of at least 12-mg/day.

2.3. Strain et al. (1994a,b)

2.3.1. Subjects and methods

This was a 26-week, double blind, double-dummy, variable dose comparison study, conducted at Johns Hopkins University in Baltimore. One hundred sixty-four (164) treatment-naïve subjects meeting DSM-III-R criteria for opiate dependence were randomly assigned to receive either sublingual liquid buprenorphine or oral methadone (with corresponding placebo). Subjects were stabilized on either 50-mg/day methadone or 8-mg/day buprenorphine, with dose changes allowed from weeks 3 through 16 of treatment. Subjects whose urines were positive for opiates or cocaine and those who requested a higher dose were given gradual increases (2-mg/day buprenorphine or 10-mg/day methadone) until achieving an optimal dose response or reaching the maximum allowable dose (16-mg/day buprenorphine or 90-mg/day methadone). Subjects whose urines were free of opiate or who reported excessive medication effects could have their dose lowered. No take-home doses were permitted. Outcome measures included illicit drug use, as measured by thrice weekly urinalyses, retention in treatment, and self-report of drug use. The ASI was administered and analyzed at weeks 0, 6 and 16, and at the end of the study. Individual counseling and weekly group therapy were offered. Subjects who missed medication for 3 consecutive days were dropped from the study. During the last 10-study-weeks, subjects were tapered from the medication at a weekly rate of 10% of their current daily dose.

2.3.2. Results

Buprenorphine and methadone were both effective on measures of treatment retention (56% in both groups), clinic attendance, and medication and counseling compliance. Opiate positive urines were 40% for both the buprenorphine and methadone groups across the maintenance period of the study. Additionally, 55% of the methadone subjects and 47% of the buprenorphine subjects abstained from opiates for 2 or more weeks. A similar number of dose increases were requested for the two treatment groups and a similar response rate was observed. The mean maintenance dose was 8.9-mg/day buprenorphine and 54-mg/day methadone. Both groups attained a 56% (43 buprenorphine and 43 methadone) retention rate through the 16-week-flexible dosing period. Additionally, there were no significant differences in cocaine or benzodiazepine use.

2.3.3. Conclusion

The investigators concluded that flexible dosing closely approximated clinical practice and that it appeared effective in suppressing opiate, but not cocaine, use. Study results supported the effectiveness of buprenorphine for treatment of opiate dependence and demonstrated its efficacy comparable to methadone when a clinically guided flexible dosing procedure is utilized.

2.4. Ling et al. (1996)

2.4.1. Subjects and methods

This 1-year-trial, conducted at Pizarro Treatment Center near downtown Los Angeles, compared 8-mg/day sublingual liquid buprenorphine with 30- and 80-mg/day methadone. Two-hundred-twenty-five subjects (46 women, 179 men) between the ages of 18 and 65, who met DSM-III-R criteria for opiate dependence and FDA criteria for methadone maintenance, were randomly assigned in equal numbers to one of three

treatment groups and treatment was conducted in double-blind fashion. Subject candidates with a DSM-III-R diagnosis of cocaine, amphetamine, alcohol or other sedative-hypnotic dependence (including benzodiazepines) were excluded from the study. Subjects who were hospitalized or briefly incarcerated during the trial were switched to 40-mg/day methadone and those who missed seven consecutive clinic visits were dropped from the study. Subjects who continued to provide opiate positive urines at weeks 7 and 8 were also dropped, and switched to a rescue protocol. Objective and subjective measures of efficacy (urine toxicology, retention, craving, and withdrawal symptoms) were analyzed at midpoint and at termination, and safety data were tabulated over the entire 52 weeks. For purposes of direct comparison with the Johnson et al. (1992) study results, efficacy data covering the first 17 weeks of treatment were analyzed and reported.

2.4.2. Results

Treatment retention was significantly greater for the high dose methadone group and similar for the buprenorphine and low dose methadone groups at both 26 and 52 weeks. A similar number of opiate-negative urine samples was observed in the buprenorphine and low dose methadone groups at both time points, with significantly more opiate negative urine samples observed in the high dose methadone group. Subjects assigned to the high dose methadone group also reported significantly less craving than the low dose methadone or the buprenorphine group. No significant adverse effects were attributed to buprenorphine.

2.4.3. Conclusion

The investigators found 8-mg/day buprenorphine to be less effective than 80-mg/day methadone, but comparable to 30-mg/day methadone for treatment of opiate dependence. No significant health risks were apparent with long-term buprenorphine maintenance at this dose. It was suggested that further studies were needed to reconcile their findings with those reported by other groups.

2.5. Schottenfeld et al. (1997)

2.5.1. Subjects and methods

This 24-week-study was designed to compare the effectiveness of higher buprenorphine and methadone maintenance doses to lower maintenance doses in reducing illicit opiate use. Additionally, the study examined whether buprenorphine is superior to methadone for reducing cocaine use. A total of 116 subjects meeting DSM-III-R criteria for both opiate and cocaine dependence were randomly assigned, in double-blind fashion, to receive either 4- or 12-mg/day sublingual liquid buprenorphine or 20- or 65-mg/day methadone. Outcome measures included retention in treatment and illicit opiate and cocaine use as determined by twice weekly urine toxicology screens and self-report. An opiate withdrawal symptom checklist was also administered once weekly.

2.5.2. Results

There was a significant difference between the high-dose and the low-dose groups in the rate of opiate positive urine samples but no significant difference was observed in treatment retention or cocaine use. The lowest opiate positive toxicology (45%) was evidenced by the 65-mg/day methadone group, followed by the 12-mg/day buprenorphine group (58%), the 20-mg/day methadone group (72%), and the 4-mg/day buprenorphine group (77%). During the first 6-weeks of the study, opiate use decreased in all treatment groups, but the decline continued during the remaining 18 weeks only in the high dose methadone and buprenorphine groups and increased slightly in both low dose groups. Maintenance with 4-mg/day buprenorphine was associated with the least favorable outcome on measures of retention and illicit use of opiates and cocaine.

2.5.3. Conclusion

The investigators found that higher maintenance doses of methadone and buprenorphine were superior to lower maintenance doses in reducing illicit opiate use, but not in reducing cocaine use.

2.6. Uehlinger et al. (1998)

2.6.1. Subjects and methods

This flexible-dose study, conducted at three outpatient clinics in Switzerland, compared the efficacy and safety of buprenorphine and methadone. Utilizing a double blind, parallel group design, 58 subjects were randomly assigned to receive either sublingual buprenorphine tablets (4–16-mg/day) or methadone (30–120-mg/day) over a 6-week-period ($n = 27$ and 31, respectively). During the first three treatment weeks all subjects were inducted to the medication dose on which they would remain during the 3-week-maintenance period. Those in the buprenorphine group were given a 4 mg sublingual tablet on days 1–3, to be increased to 8 mg on day 4 if signs of withdrawal were present or decreased to 2 mg if opiate intoxication was apparent. On day 8, the buprenorphine dose could be increased to 12 mg and on day 15 to the maximum 16-mg/day dose. Subjects in the methadone group were started on 30-mg/day methadone and allowed adjustments according to the same schedule and criteria as used for buprenorphine, to a maximum dose of 60 mg on day 4, 90 mg on day 8, and 120 mg on day 15. At the end of the third week, all subjects were considered to have reached their maintenance dose, which remained fixed over the next

21 days. Objective and subjective measures of efficacy were monitored weekly and safety measures were monitored on a regular basis throughout the trial. Primary outcome measures were treatment retention, illicit opiate use as measured by randomly collected once weekly urine specimens, with missed specimens considered positive, and self-report of drug use and opiate craving. Subjects who missed 3 consecutive days of medication were dropped from the study. After completion of the 6-week-study, subjects were either detoxified or remained on buprenorphine or methadone treatment.

2.6.2. Results

At the end of week 6, the mean medication doses were 10.5-mg/day buprenorphine and 69.8-mg/day methadone. Overall, 74% of the subjects completed the study. Retention was significantly better for the methadone group (90%) compared with the buprenorphine group (56%). However, a majority of the buprenorphine dropouts occurred during the first 10 days of treatment, leading the investigators to hypothesize that the early buprenorphine dose might have been too low for highly opiate dependent patients. Among subjects remaining in treatment there was no significant difference between the buprenorphine and methadone groups in percentage of positive urine specimens (62 and 59%, respectively). Opiate craving decreased significantly during the treatment period for both groups. No serious adverse events occurred in either group. At the end of the study, three of 15 buprenorphine subjects switched to methadone and one of 28 methadone subjects switched to buprenorphine.

2.6.3. Conclusion

The first to compare the buprenorphine tablet formulation to standard liquid methadone, this study suggested that it might be more difficult to begin treatment with buprenorphine than with methadone in highly opiate dependent patients. However, since both medications were comparable once a maintenance dose was reached, the investigators speculated that it might be necessary to induct patients more rapidly onto buprenorphine than methadone, use more frequent dose adjustments, or use more equivalent doses, i.e. start treatment at a higher dose with the buprenorphine tablets. It appeared that buprenorphine could be a viable alternative to methadone with a more adequate induction schedule. The investigators noted that the study was limited by the short, 3-week-maintenance period, by comparison of non-equivalent doses, and by the small sample size. It was felt that further investigation into the different dose-related effects of buprenorphine seen in particular subsets of addicts might be warranted.

2.7. Johnson et al. (2000)

2.7.1. Subjects and methods

This 17-week, double-blind study compared levomethadyl acetate (LAAM) (75-100 mg three-times/week), buprenorphine (16-32 mg as a sublingual solution three-times/week), high-dose (60–100-mg/day) methadone and low-dose (20-mg/day) methadone as treatments for opiate dependence. Two-hundred twenty subjects meeting DSM-IV criteria for opiate dependence were randomly assigned, in equal numbers, to one of the four treatment groups, with randomization of the last ten subjects constrained to achieve 55 subjects per group. Except for the low dose methadone (control) group, all doses were individualized. Patients attended the clinic daily during the 2-week induction period and received gradually increasing doses. Those on LAAM were given 25 mg on day 1 and then began alternating between placebo and LAAM, increasing by 10 mg until the 75 mg LAAM dose was reached. Those on buprenorphine were given 4 mg on day 1, increasing to 8 mg on days 2–7, and then alternating between placebo and 16 mg buprenorphine. Beginning on week 3, patients attended clinic on Monday, Wednesday and Friday and were given bottles of medication to take at home on the other 4 days. Subjects on LAAM, buprenorphine, and high-dose methadone could receive blinded dose increases starting in week 3 if they met predetermined criteria. Those subjects with poor responses to LAAM or buprenorphine were switched to methadone. Primary outcome measures were retention in treatment, opiate use as measured by urine toxicologies and degree of continued opiate abstinence, and subject's global ratings of drug problem severity.

2.7.2. Results

Treatment retention was significantly higher for the LAAM, buprenorphine, and high dose methadone groups than for those receiving low-dose methadone. Continued participation was significantly higher for the high-dose methadone group than for those on LAAM. The percentage of subjects with 12 or more consecutive urine specimens negative for opiates was 36% in the LAAM group, 26% in the buprenorphine group, 28% in the high-dose methadone group, and 8% in the low-dose methadone group. On a scale of 0–100, subjects in the LAAM group reported a mean score of 35 as the severity of their drug problem at the time of their last report. Those in the buprenorphine group reported a mean score of 34, while the high-dose methadone group reported a mean score of 38 and the low-dose methadone group reported a mean score of 53.

2.7.3. Conclusion

The investigators concluded that, compared with low-dose methadone, LAAM, buprenorphine and high-dose

methadone may substantially reduce the use of illicit opiates.

3. Buprenorphine versus methadone detoxification

"Detoxification" as defined in the present context means assisting street heroin addicts to become abstinent or discontinuing patients from opiate maintenance. An effective medication for detoxification should suppress withdrawal symptoms sufficiently to allow an opiate dependent person to become opiate-free. Few studies have adequately examined buprenorphine for opiate detoxification and only one made a direct comparison with methadone.

3.1. Bickel et al. (1988)

3.1.1. Subjects and methods

This 90-day, double-dummy, double-blind trial involved 45 heroin users randomly assigned to receive either 2-mg/day sublingual liquid buprenorphine or 30-mg/day oral methadone for 3 weeks, followed by 4 weeks of dose reductions and 6 weeks of placebo. Urine samples were tested for opiates and self-reports of withdrawal symptoms and opiate effects were obtained. To compare the ability of buprenorphine and methadone to block the subjective and physiological effects of an opiate, a 6-mg intramuscular hydromorphone challenge was administered during week 2 of the trial.

3.1.2. Results

No significant differences between groups were found on measures of retention, illicit opiate use, or self-report of symptoms. Methadone attenuated opiate effects on both physiological (pupil constriction) and self-report measures to a greater degree than buprenorphine on hydromorphone challenge, but this did not result in greater abuse of illicit opiates by subjects in the buprenorphine group.

3.1.3. Conclusion

Buprenorphine appeared both acceptable to patients and as effective as methadone in the detoxification of heroin addicts (for more detailed discussion of detoxification see Johnson et al., 2003; Walsh and Eissenberg, 2003).

4. Buprenorphine versus placebo

Among the series of controlled clinical trials with buprenorphine, three may be regarded as placebo-comparison studies. Two used a true inert placebo while a third used 1 mg buprenorphine as an active placebo in a multi-dose ranging study.

4.1. Johnson et al. (1995)

4.1.1. Subjects and methods

This study was designed to assess the early clinical effectiveness (1–2 weeks) of buprenorphine compared with placebo. Utilizing a double-blind, parallel-group design, 150 subjects were randomly assigned to receive either 2-mg/day ($n = 60$) or 8-mg/day ($n = 30$) sublingual liquid buprenorphine or placebo ($n = 60$) over a period of 14 days. During days 6–13 subjects could request a change in group assignment, which would be randomly chosen from one of the two alternatives and implemented on the following day. Subjects could then continue on the alternate regimen through day 14. Primary outcome measures were days on initial dose and percentage of subjects requesting a dose regimen change.

4.1.2. Results

Subjects treated with buprenorphine, independent of dose, showed greater time on initial dose (10–11 vs. 8 days), requested fewer dose changes (27, 32, 65%, respectively), used less illicit opiates and reported higher ratings of medication adequacy than those treated with placebo. The 2- and 8-mg/day buprenorphine groups were comparable on all outcome measures.

4.1.3. Conclusion

Sublingual buprenorphine was clearly more effective than placebo during the initial days of treatment for opiate dependence. The investigators also concluded that a placebo-controlled study with a behavioral choice component would be an effective means of assessing the potential efficacy and acceptability of new pharmacotherapies for opiate dependence.

4.2. Ling et al. (1998)

4.2.1. Subjects and methods

This was a 12-site, double-blind, randomized trial designed to evaluate the safety and efficacy of 8-mg/day sublingual liquid buprenorphine compared with 1-mg/day sublingual liquid buprenorphine in maintenance treatment of opiate dependence. Although this study compared four buprenorphine doses (1, 4, 8, 16 mg), the primary indicator of efficacy was the difference in outcome between the 8 and 1 mg groups, as had been agreed to by the investigators after consultation with the FDA. The other two dose groups were added to provide additional dosing safety information. Seven-hundred thirty-six heroin users (239 female; 497 male) who met DSM-III-R criteria for opiate dependence and had been using opiates daily for at least 6 months prior to study start-up were enrolled in the trial. Following randomization to one of the four dose groups, subjects were rapidly inducted over a 5-day-period to their assigned daily dose on which they were maintained for 16 weeks.

Subjects attended clinic daily and were offered weekly counseling during the treatment period. Primary efficacy measures were retention in treatment, illicit opiate use as determined by three-times-a-week urine toxicology, opiate craving, and global rating by subjects and staff. Clinical monitoring and reports of adverse events were included as safety outcome measures. Analysis of efficacy and safety was performed at 16 weeks.

A safety extension phase of this study allowed treatment to be continued to a full 52 weeks, after which further safety analysis was performed. Three-hundred thirty-two subjects elected to enter the 36-week-extension, during which double-blind dose adjustments were allowed, to a maximum of 32-mg/day buprenorphine.

4.2.2. Results

A total of 375 subjects (51%) across sites completed the 16-week-parent study. Significantly more subjects on 8 and 16-mg/day buprenorphine completed treatment compared with those receiving 1-mg/day. Subjects treated with 16-mg/day buprenorphine were much more likely to provide 13 consecutive opiate negative urine samples than those treated with either 1- or 4-mg/day and there was more sustained abstinence in the higher dose group. No increase in adverse effects was seen with increased doses. Craving was lower in the 8-mg/day group than in the 1-mg/day group. The most common reason for termination was "no show" (43%). Twenty-five subjects terminated due to "adverse effects" and 85 (24%) were terminated for reasons unrelated to the study or medication (e.g. three due to pregnancy).

During the extension phase some of the clinics were not open 7 days a week resulting in some missed doses. Thus, the mean doses actually received were often less than those prescribed. Moreover, although all subjects could have their dose increased to the maximum dose of 32-mg/day, there was a wide distribution of maintenance doses during this phase. No dose escalation was noted over the 52-week-period.

4.2.3. Conclusion

Based on the primary efficacy measures and all of the secondary efficacy parameters, the investigators concluded that 8-mg/day buprenorphine was more effective than 1-mg/day. Buprenorphine maintenance was found to reduce illicit heroin use and alleviate craving, indicating that it is safe and effective for long-term treatment of opiate dependence.

The extension phase suggested that sublingual buprenorphine in the range of 1–32-mg/day was safe for use over extended periods. The investigators felt that it would be reasonable to initiate treatment on 4-mg/day with stepwise increases of 2-mg/day, to a total of 16-mg/day if needed. Increases to above 16-mg/day appeared to be of limited clinical benefit.

4.3. Krook et al. (2001)

4.3.1. Subjects and methods

This 12-week, randomized, double-blind study conducted in Oslo, Norway, was designed to evaluate whether buprenorphine (administered as sublingual tablets), when provided without additional control and psychosocial treatment and support, alleviates the problems of patients waiting for medication assisted rehabilitation. One-hundred six subjects with an average age of 38 years and a 20-year-average history of heroin use were assigned to receive either 16-mg/day buprenorphine ($n = 55$) or placebo ($n = 51$). Double doses were given on Saturdays and there was no dosing on Sundays. Outcome measures included treatment retention, compliance, as indicated by total number of doses taken, self-report of drug use, recorded as 0–10 on a visual analogue scale, and subject's wellbeing and mental health, as measured on a 0–10 visual analogue scale.

4.3.2. Results

The average number of participation days was significantly higher for the buprenorphine group (42) compared with the placebo group (14). Sixteen subjects in the buprenorphine group remained in the study after 12 weeks compared with one in the placebo group. Decrease in reported opiate use was also more notable in the buprenorphine group ($P < 0.001$) than in the placebo group ($P < 0.01$), and the buprenorphine group had greater improvement in their sense of well being ($P < 0.01$) and life satisfaction ($P < 0.05$). No significant adverse events or deaths were reported during the study and side effects were those generally expected with buprenorphine.

4.3.3. Conclusion

The investigators found that when given buprenorphine as an interim therapy, patients waiting for medication assisted rehabilitation benefit significantly in terms of treatment retention, self-reported drug use, and sense of well-being. Without psychosocial support, however, subjects had difficulty remaining in treatment over time.

5. Comments

Of the buprenorphine/methadone comparison studies, three utilized a fixed dose design, two used a variable dose, and one used a four-dose comparison. The Johnson et al. (1995) study was the only true placebo controlled trial of buprenorphine maintenance. The Ling et al. (1998) study, which used a four-dose comparison, was both a dose comparison and a placebo-controlled trial. When the study was planned, the best data then in existence suggested that 8 mg of

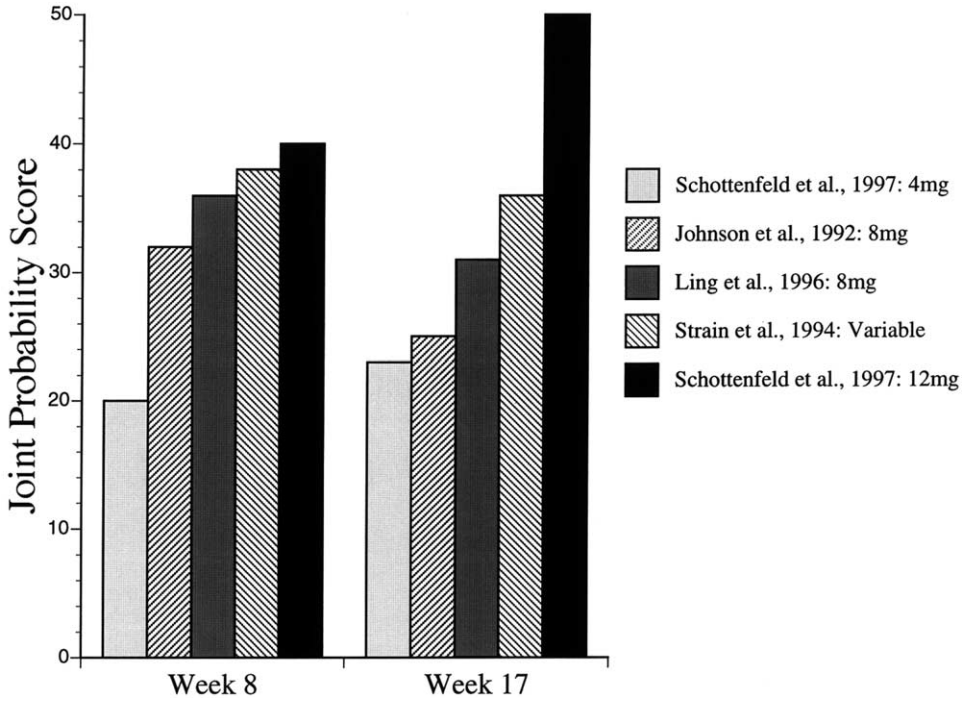

Fig. 1. The efficacy of buprenorphine for treatment of opiate dependence compared across studies and as a function of buprenorphine dose. Efficacy was measured by the JP Score, which combines treatment retention and urinalysis outcomes. Outcomes are shown for both 8 and 17 weeks of treatment.

buprenorphine was roughly comparable to 60 mg of methadone. The planning group, by agreement with the FDA, decided to use 8:1 mg buprenorphine as the primary outcome, regarding the 1-mg buprenorphine dose as an active placebo. The 4 and 16 mg doses were added to gather additional dosing and safety information but all analyses involving those two doses were to be regarded as secondary outcomes. The study results clearly showed the 8-mg buprenorphine dose to be superior to the 1-mg dose by every measure, although there were some subjects who appeared to do well even with the 1-mg dose. There was an undisputed dose response curve showing the efficacy of buprenorphine and the superiority of doses above 8 mg.

A number of outcome measures were utilized in these studies, common among them were retention, drug use, and global rating, although these were not used consistently throughout. For example, the Johnson et al. (1992) study adopted the Mantel–Haenszel method for analysis of the urine results whereas others, like Kosten et al. (1993), Strain et al. (1994a,b), used analysis of variance for repeated measures. The Ling et al. (1996) study used what has come to be called the treatment effectiveness score (TES), counting the number of clean urines collected over the course of the study with the number of urines projected to be collected as the denominator (Ling et al., 1995). Still, other investigators compared the number of patients able to achieve three or 4 consecutive weeks of clean urines. All of these methods looked at urine results in slightly different ways and carry with them different strengths and weaknesses.

To compare results across studies, the Ling group used the joint probability (JP) index. This index is the product of a patient's probability of being in treatment (P_1) and of not using heroin or yielding a "clean" urine (P_2) at certain time points in the trial. Using the P_1P_2, the group compared results of several studies for which data were available (Johnson et al., 1992; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994a,b) and examined drug use in similar fashion. All of the studies had treatment duration of at least 16 weeks. A clear dose–response curve was shown with a greater number of patients performing well on the index as the buprenorphine dose increased (see Fig. 1). A similar observation can be made with the methadone dose used in these studies. Interestingly, on this index the high dose methadone group in the Johnson study appears to be an under-performing group. This gave the buprenorphine 8-mg group an apparent advantage and makes it appear superior to 60-mg methadone. Other studies, however, showed 8-mg buprenorphine to be less effective than 60-mg methadone. Of note also is that a finding of "no significant difference" is often loosely interpreted to mean clinical equivalency, which it is not.

Overall, this series of studies did firmly establish the efficacy of buprenorphine alone and in comparison to

methadone. Few serious adverse events were reported, attesting to buprenorphine's high safety profile and in keeping with its pharmacological characteristics.

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